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Nickel-Catalyzed Oxidative Decarboxylative (Hetero)Arylation Reactions

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Abstract

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Aaron Honeycutt

Transition-metal-catalyzed decarboxylative coupling reactions have gained considerable attention over the past decade as an efficient route to form heterobiaryls. However, current methods for oxidative decarboxylative (hetero)arylation with unactivated C–H bonds have been limited by poor substrate scope, control of regioselectivity, and chemospecificity. This thesis describes the development of a new nickel-catalyzed oxidative decarboxylative coupling (ODC) with unactivated C–H bonds. The first chapter discusses the development of the new nickel-catalyzed ODC reaction to enable the coupling of a N,N′–bidentate directing group with a broad scope of heteroaromatic carboxylates and *ortho*-substituted benzoates, a scope that has not been achieved in previous oxidative decarboxylative coupling transformations. The following chapter is an extension of the nickel-catalyzed ODC reaction for the synthesis of heterocycle-containing phenanthridinones. This chapter details an oxidative decarboxylative annulation with heteroaromatic carboxylates and *ortho*-fluorobenzoates. The final chapter describes the investigation and attempted synthesis of a proposed Ni(II) metallacycle from our catalytic cycles in the previous chapters. Synthesis of a Ni(II) metallacycle by denitrogenation of 3-(quinolin-8-yl)-3,4-dihydro-1,2,3-benzotriazin -4-one led to an interesting azanickelacycle dimer. However, decarbonylation of a 2-(quinolin-8-yl)-2,3-dihydro-1H-isoindole-1,3-dione led to the desired five-membered metallacycle. Each of these chapters represents the challenges to developing an oxidative decarboxylative arylation with unactivated C–H bonds with a first-row transition metal.

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Å:	Ångstrom
acac:	Acetylacetonate
AcOH:	Acetic acid
ATR:	Attenuated total reflection
BQ:	1,4-Benzoquinone
C:	Celsius
calcd:	Calculated
cat.:	Catalyst
COD:	Cyclooctadiene
Cp:	Cyclopentadienyl
Cy:	Cyclohexyl
DCM:	Dichloromethane
dcpe:	Bis(dicyclohexylphosphino)ethane
DG:	Directing group
DHA:	9,10-Dihydroanthracene
DMA:	*N*,*N*-dimethylacetamide
DMF:	*N*,*N*-dimethylformamide
DMSO:	Dimethyl sulfoxide
Dppbenz:	1,2-Bis(diphenylphosphino)benzene
Et:	Ethyl
equiv:	Equivalent
ESI:	Electrospray ionization
FT-IR:	Fourier transform infrared spectroscopy
g:	Gram
h:	Hour
Het:	Hetero
HRMS:	High-resolution mass spectrometry
IMes·HCl:	1,3-Bis(2,4,6-trimethylphenyl)imidazolium Chloride

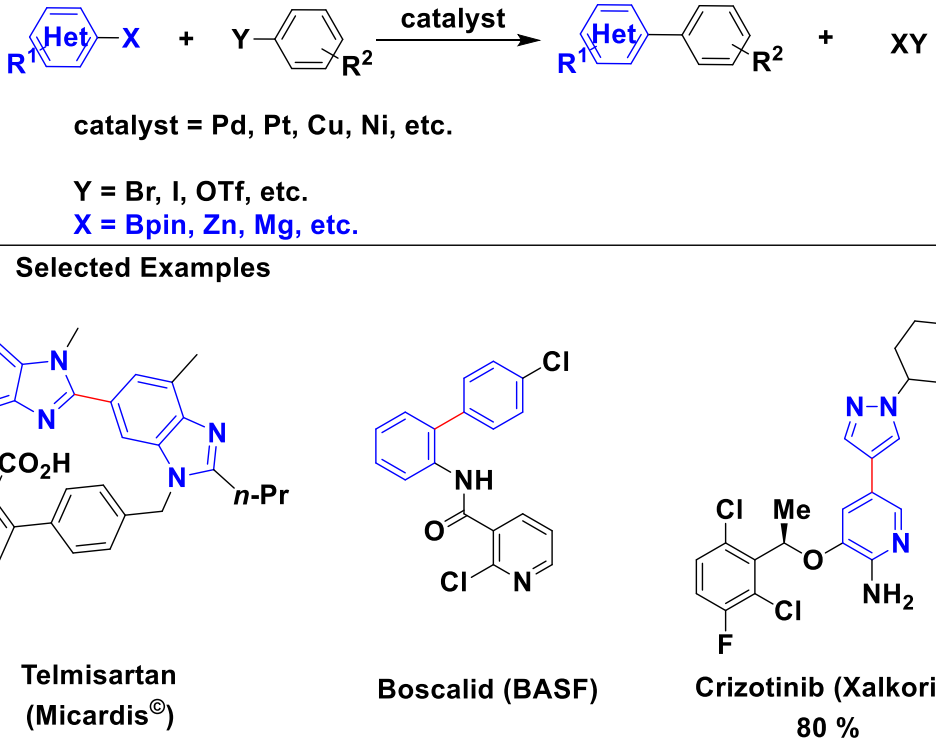
*i*Pr:	Isopropyl
L:	Ligand
OAc:	Acetate
OTf:	trifluoromethylsulfonate
Me:	Methyl
MHz:	Megahertz
mol:	Mole
mp:	Melting point
m/z:	Mass to charge ratio
M.S.:	Molecular sieves
NFSI:	*N*-fluorobenzenesulfonimide
NMP:	*N*-methyl-2-pyrrolidone
NMR:	Nuclear magnetic resonance
ODC:	Oxidative decarboxylative coupling
PCy_3:	Tricyclohexylphosphine
Ph:	Phenyl
phen:	1,10-Phenanthroline
PivOH:	Trimethylacetic acid
PPh_3:	Triphenylphosphine
ppm:	Parts per million
Q:	Quinolyl
S:	Solvent
S-Phos:	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
TBAI:	Tetrabutylammonium iodide
*t*Bu-XPhos:	2-Di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl
TEA:	Triethylamine
TEMPO:	2,2,6,6-tetramethyl-1-piperidinyloxy
TFA:	Trifluoroacetate
TfOH:	Trifluoromethanesulfonic acid
THF:	Tetrahydrofuran

THP:	Tetrahydropyran
TMSO:	3-(trimethylsilyl)-2-oxazolidin

Chapter 1: Introduction

1.1. Traditional Cross-Coupling Systems for Unsymmetrical Biaryls

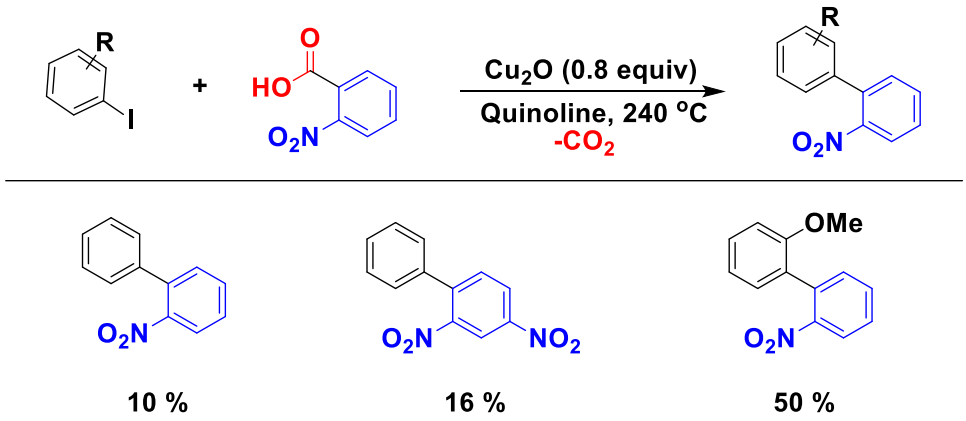
Transition-metal-catalyzed cross-coupling reactions have gained considerable attention over the past thirty years for the construction of unsymmetrical biaryls.[1] These well-known reactions such as the Suzuki-Miyaura, [2] Kumada, Negishi,[3] and Mizoroki-Heck[4] coupling reactions were developed for building various unsymmetrical biaryls (Scheme 1).[5] These reactions have allowed chemists to construct complex pharmaceutical building blocks, increase industrial process development, and advance material sciences. However, these traditional cross-coupling methods require prefunctionalized aryl halide or pseudohalide coupling partners thereby resulting in poor atom- and step-economy. On the contrary, decarboxylative coupling reactions for biaryl formation would eliminate the need for prefunctionalized aryl halide or pseudohalide coupling partners because, carboxylic acids are ubiquitous in nature, commercially available in a large scope, and easy to handle.



Scheme 1. Traditional transition-metal-catalyzed cross-coupling for the synthesis of biaryls.

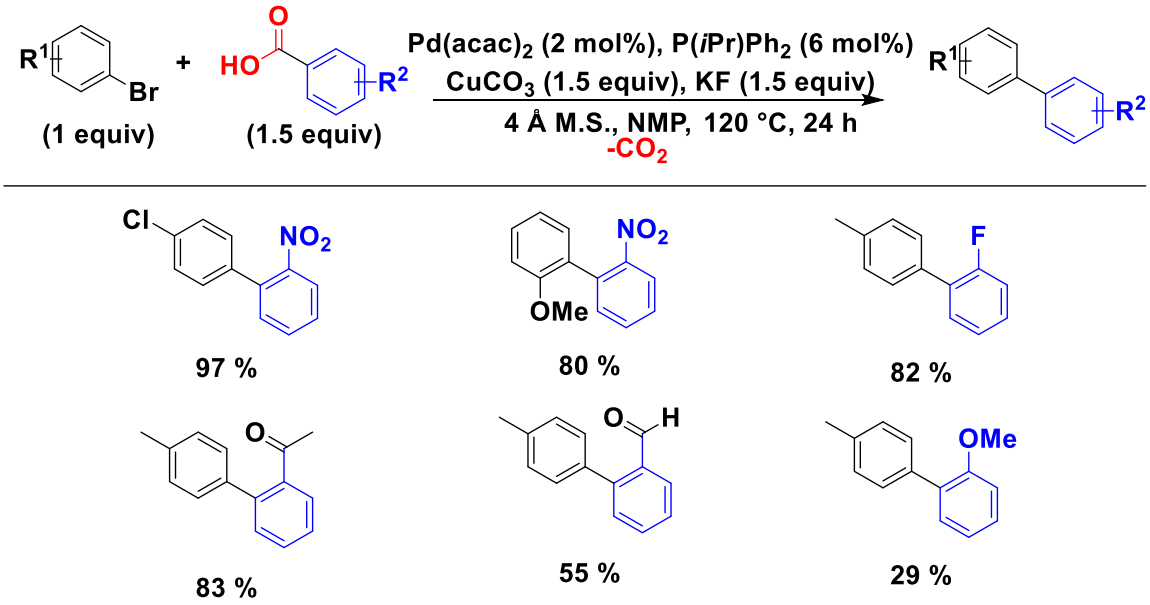
1.2. Decarboxylative Coupling Reactions for the Synthesis of Biaryls

The first reported decarboxylative Ullmann-type coupling for the synthesis of biaryls was from Nilsson in 1966.[6] Nilsson found that benzoic acids undergo decarboxylative coupling in the presence of stoichiometric amounts of copper and aryl iodides (Scheme 2). However, the reaction was limited to only *ortho*-nitrobenzoic acids and product yields were low due to harsh reaction conditions. However, this new method demonstrated the viability of using benzoic acids as nucleophilic coupling partners.



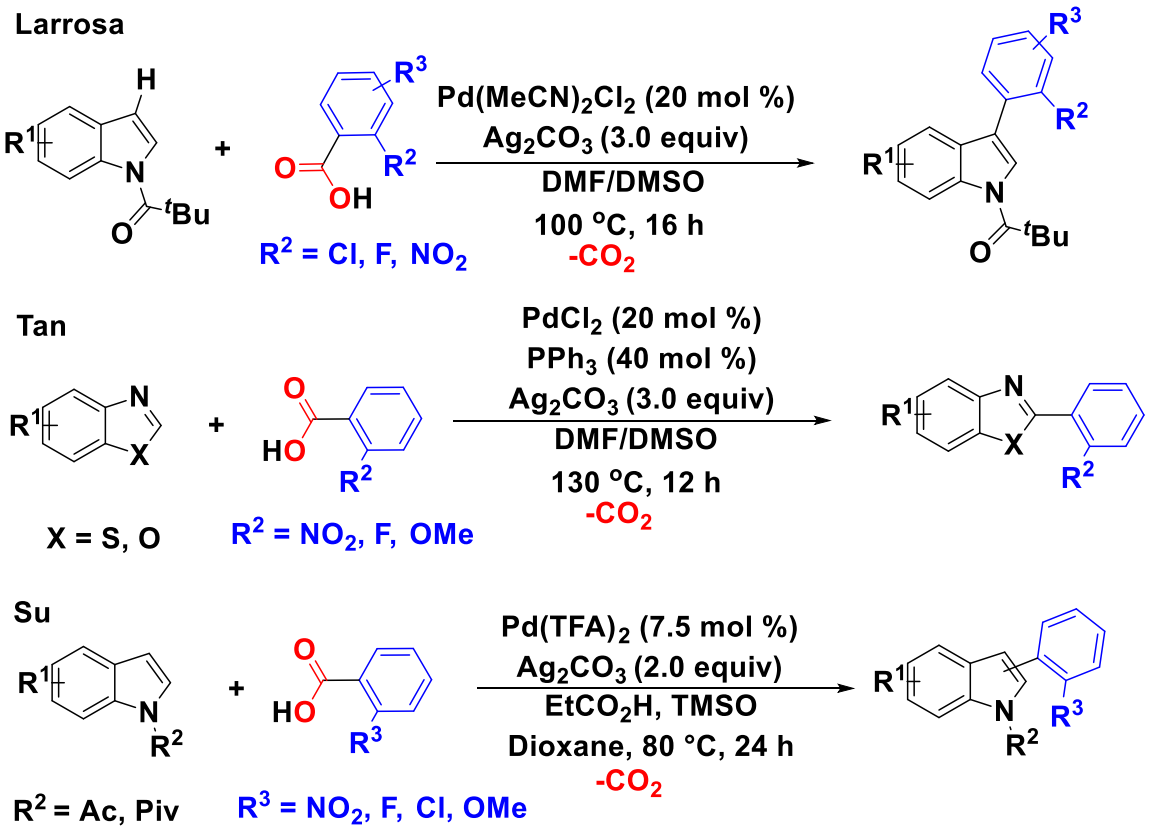
Scheme 2. Decarboxylative Ullmann coupling for the synthesis of biaryls with copper.

The first catalytic decarboxylative cross-coupling reaction was not reported until forty years later. In 2006, Goossen and co-workers reported the first example of a bimetallic palladium/copper-catalyzed redox neutral decarboxylative cross-coupling of aromatic carboxylic acids with aryl halides (Scheme 3).[7] This new method afforded unsymmetrical biaryls in good yields. However, this system is limited to *ortho*-substituted benzoic acids such as the 2-nitro, 2-fluoro, 2-methoxy, and 2-acetylbenzoic acids, for example.



Scheme 3. A bimetallic redox-neutral decarboxylative coupling of aryl halides with benzoic acids.

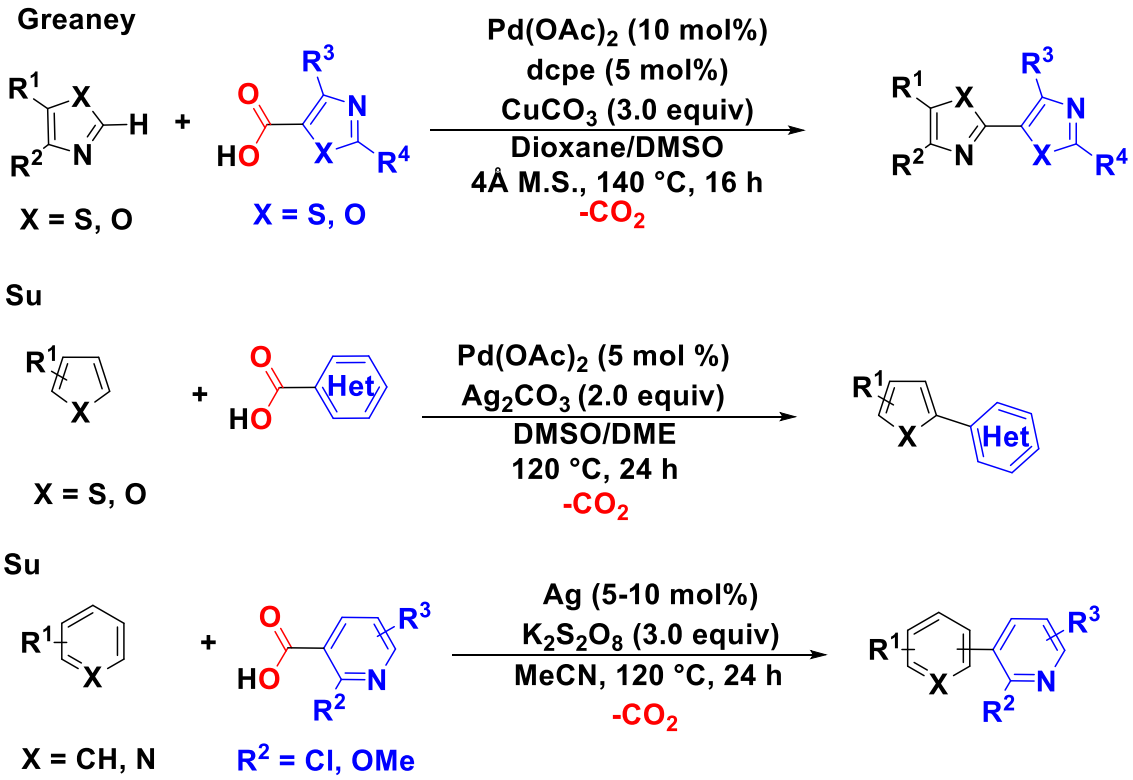
Though Goossen and co-workers disclosed the first catalytic redox-neutral decarboxylative coupling, this reaction still requires the use of prefunctionalized aryl halides and pseudohalides as coupling partners. Efforts that are more recent have led to oxidative variants of these coupling reactions which would enable the coupling of arene C–H bonds thereby eliminating prefuntionalized coupling partners. In 2008, Crabtree and co-workers reported the first Pd-catalyzed intermolecular and intramolecular decarboxylative arylation of C–H bonds.[8] Following this seminal work, other groups such as Larrosa[9], Tan[10], and Su[11] have developed related oxidative decarboxylative coupling (ODC) reactions with C–H bonds (Scheme 4) and have found that the strategies are typically limited in their substrate scope.



Scheme 4. Oxidative decarboxylative couplings with activated C–H bonds.

The majority of oxidative decarboxylative couplings employ Pd catalysts. However, most of these catalyst systems are limited to *ortho*-substituted benzoic acids. The

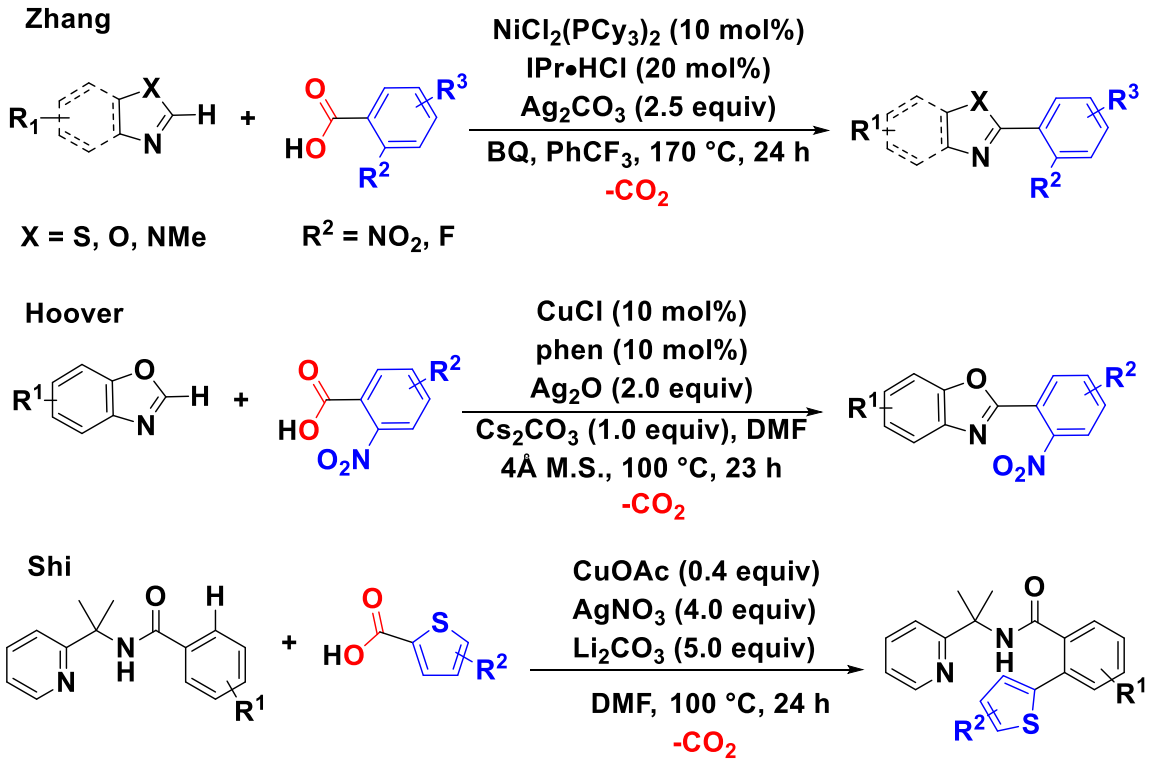
decarboxylative coupling of heteroaromatic carboxylic acids would be attractive as heterobiaryl structures are common motifs in pharmaceutically relevant compounds,[12] and the corresponding esters are the direct products of traditional heterocycle syntheses.[13] Notably, Greaney[14] and Su[15] reported the first ODC reactions of heteroaromatic acids; yet, they were limited to reactions with activated C–H bonds such as oxazoles and thiophenes. A silver-mediated oxidative decarboxylative C–H arylation that enables the coupling of pyridine carboxylic acids through a radical pathway has also been reported by Su, but shows poor regioselectivity (Scheme 5).[16]



Scheme 5. Selected examples of oxidative decarboxylative coupling reactions of heteroaromatic carboxylic acids.

Recently, there has been interest in replacing noble-metal catalysts with base-metals in ODC reactions. However, many of these reactions that use copper-[17] or nickel-[42] catalysts are again limited to the coupling of 2-nitrobenzoic acids and pentafluorobenzoic acids with arenes bearing activated C–H bonds. The one exception is a recent report of a copper-catalyzed ODC reaction from Shi and co-workers.[18] They found their reaction

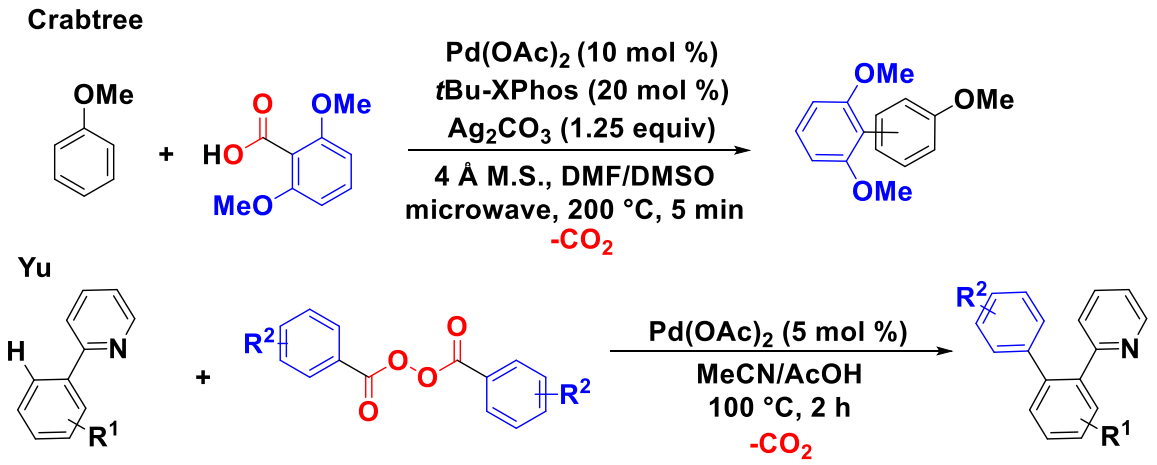
method would couple 2-thiophene carboxylic acids. However, during their mechanistic studies they found the reaction proceeded through a protodecarboxylation and dehydrogenative coupling with complete loss of chemospecificity. Overall, these reaction methods that enable the oxidative decarboxylative heteroarylation of C–H bonds with a base metal are limited to a specific class of heteroaromatics such as thiophene, azoles, and nicotinic carboxylic acids (Scheme 6).



Scheme 6. Oxidative decarboxylative coupling with base metal catalysts.

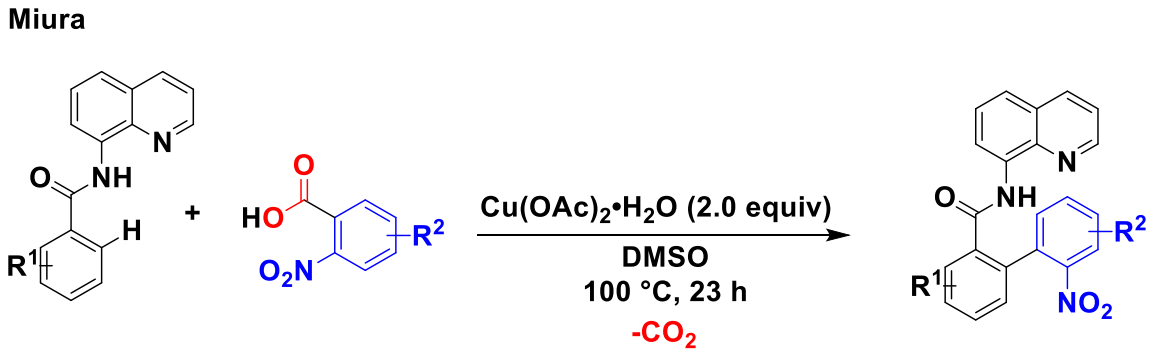
Decarboxylative arylation reactions have similar limitations with respect to the C–H coupling partner. As mentioned earlier, these reactions are often specific to couplings of electronically activated C–H bonds such as oxazoles and thiazoles. Efforts to enable the decarboxylative arylation of unactivated C–H bonds are limited. The Crabtree group[8] and Glorius[19] group reported early examples of oxidative decarboxylative coupling reactions with unactivated C–H bonds; yet, both of these transformations form regioisomeric product mixtures. It was not until 2009 that Yu and co-workers reported the first Pd-catalyzed decarboxylative arylation of arenes using 2-phenylpyridine and electron-

deficient aryl acylperoxides (Scheme 7).[20] Although this reaction allowed the installation of a broader scope of arenes not seen in previous ODC systems, the required aryl acyl peroxides are commercially limited and potentially dangerous.



Scheme 7. Oxidative decarboxylative coupling with unactivated C–H bonds.

Two copper systems have been reported recently that enable the decarboxylative coupling with arenes bearing benzamide directing groups. The first, from Shi[18] and co-workers (Scheme 6), is specific to the coupling of 2-thiophene carboxylic acids through a tandem protodecarboxylation-dehydrogenative coupling pathway resulting in the loss of regiospecificity of the acids. More recently, Miura and co-workers have reported a copper-mediated ODC reaction of benzamides, however, their reaction suffers from limitations in the acid coupling partner, and efficient coupling is only achieved with 2-nitrobenzoic acids (Scheme 8).[65]

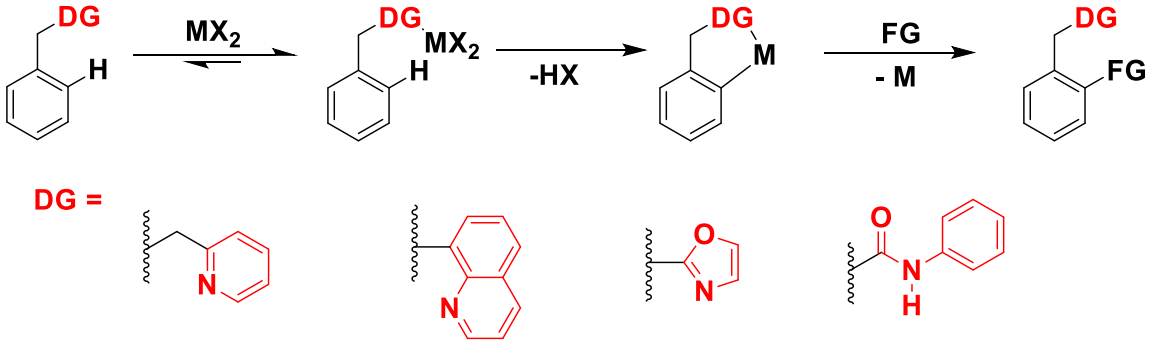


Scheme 8. Copper-mediated ODC reaction with unactivated C–H bonds and 2-nitrobenzoic acids.

There are currently no examples of a catalytic oxidative decarboxylative arylation of unactivated C–H bonds capable of coupling a broad scope of (hetero)aromatic carboxylic acids. However, this thesis will later discuss the development of a new reaction method that overcomes these limitations by paring a base metal with a silver oxidant that will be discussed in Chapters 2 and 3.

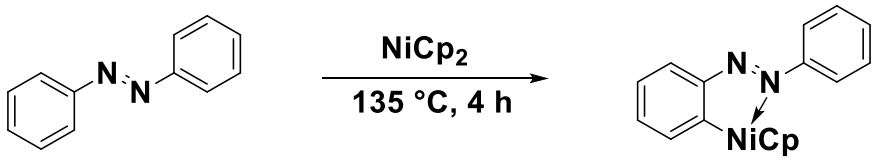
1.3. Transition-Metal Catalyzed Directing Group Assisted C–H Activation

During the last decade, C–H functionalization has been used as an invaluable technique for the installation of a plethora of functional groups in complex molecules.[21] Due to the high bond-dissociation energy of a C–H bond (110 kcal mol^{-1}), transition metals are commonly used. The activation and functionalization of inert C–H bonds with a transition metal offers an atom- and step-economical path towards building new methodologies in cross-coupling reactions. Recently, research groups have used the directing group (DG) approach for the activation of these inert C–H bonds. In this approach, the transitional metal catalyst coordinates to the monodentate directing group, increasing the reactivity due to precoordination and facilitates the formation of a thermodynamically stable metallacycle (Scheme 9).[22] This method has been applied not only to the formation of carbon-carbon bonds, but also carbon-heteroatom bonds.



Scheme 9. C–H activation and functionalization with directing groups and a transition metal.

Early development of a directed cyclometalation of C–H bonds with a group 10 metal was reported by Kleiman and Dubeck.[23] They found that when $NiCp_2$ as treated with azobenzene the formation of the cyclometalated complex cyclopentadienyl [*o*-(phenylazo)phenyl]nickel resulted (Scheme 10, Cp = cyclopentadienyl). Following this work, Cope and co-workers reported a related cyclometalation of azo compounds using $PdCl_2$.[24]

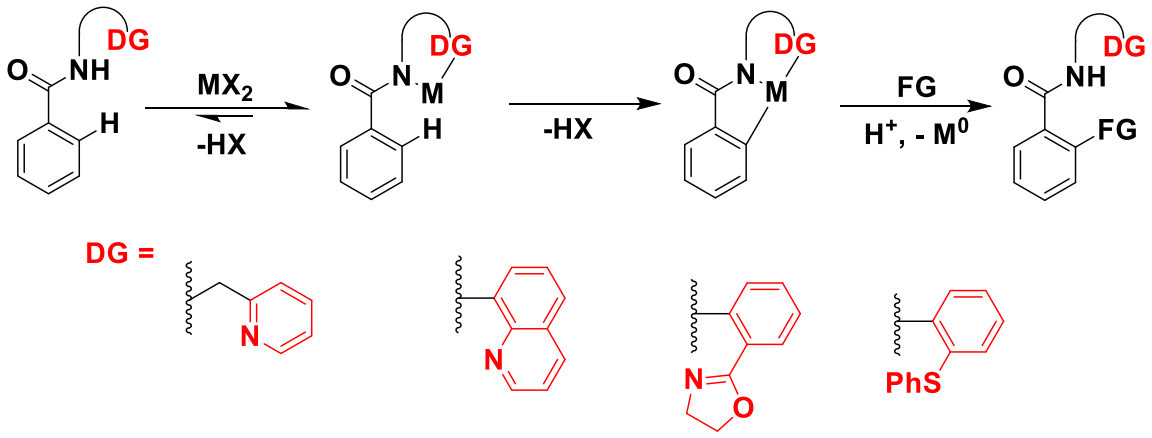


Scheme 10. First reported nickel metallacycle by C–H activation**.**

Building on these early pioneering works, many groups have focused on developing new methodologies for C–H functionalization using more sustainable and cost-effective first-row transition metals, such as Co, Ni, Fe, and Cu. However, there are fundamental challenges that first row transition metals face compared to their second and third row counter parts. First row transition metals have weaker M-C bonds making the catalytic system difficult to control upon C–H activation.[25] In addition, C–H activation with first row-metals can be more complicated since these metals are prone to single electron oxidations.

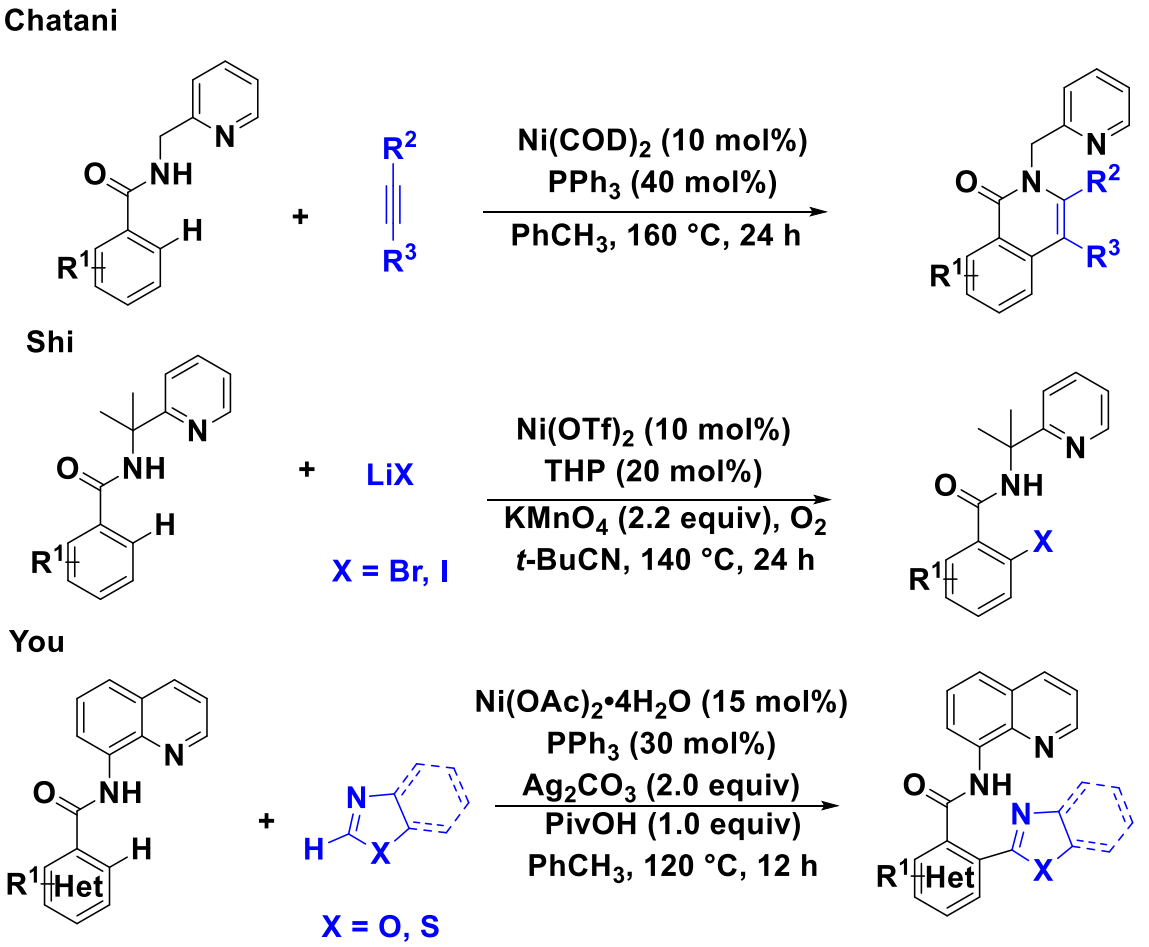
To overcome these issues, many groups have used tethered bidentate directing groups made from benzoic acid derivatives with first row-metals. These bidentate directing

groups allow for improved C–H activation because: 1) they increase the reactivity because of the higher effective concentration of the catalyst at the site of interest 2) facilitate the formation of a thermodynamically stable metallacycle upon C–H activation and 3) the metallacycle intermediate is stabilized in higher oxidation states after C–H activation (Scheme 11).[26, 27]



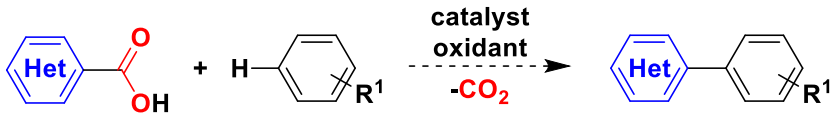
Scheme 11. Bidentate C–H activation and functionalization with a transition metal.

Recently, nickel catalysis has received increasing attention due to its promising reactivity with C–H bonds. This evidence has been shown in several examples in literature for forming C–C[32], C–N[28], and C–S[29] bonds utilizing a directing group. Initial progress in C–H functionalization reactions catalyzed by nickel are limited to the activation and coupling of specific activated C–H bonds such as polyfluorinated benzene, azoles, and pyridine derivatives.[30] However, examples of nickel-catalyzed activation of unactivated C–H bonds are limited. In 2011, Chatani and co-workers reported the first nickel-catalyzed functionalization of unactivated C–H bonds using a N,N′-bidentate directing group.[31] This led to the development of a variety of different transformations such as, arylation,[32] alkynylation,[33] alkylation,[34] halogenation,[35] dehydrogenative coupling,[36] and allylation (Scheme 12).[37]



Scheme 12. Selected examples of nickel-catalyzed directed C–H functionalization reactions.

We envisioned using a base metal in the presence of a N,N′-bidentate directing group to help facilitate the functionalization of inert C–H bonds for decarboxylative coupling. After many attempts, we finally succeed in developing a new method for the oxidative decarboxylative (hetero)arylation of unactivated C–H bonds later discussed in the following chapters.

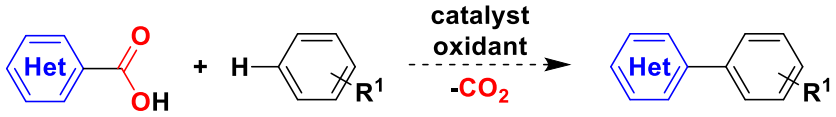


Scheme 13. The targeted ODC reaction of unactivated C–H bonds with (hetero)aromatic acids and first-row transition metal catalyst.

Chapter 2: (Hetero)Arylation of Unactivated C-H Bonds by Oxidative Decarboxylative Coupling

2.1. Overview

As seen in Chapter 1, oxidative decarboxylative couplings are becoming an attractive alternative to their redox-neutral counter parts. We initially set our goal of achieving an oxidative decarboxylative (hetero)arylation with unactivated C–H bonds with heteroaromatic carboxylic acids, since, heterobiaryls can be found in many pharmaceuticals, agrochemicals, and material sciences.[38] We hypothesized that an unactivated C–H bond could be functionalized with a heteroaromatic carboxylic acid in the presence of a base metal catalyst and oxidant (Scheme 14).



Scheme 14. Targeted goal of achieving an oxidative decarboxylative arylation with unactivated C–H bonds.

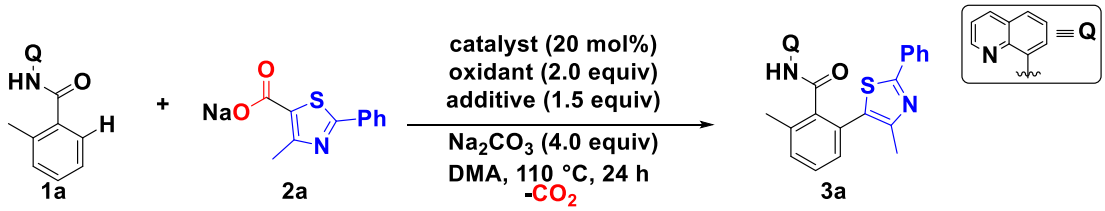
2.2. Results

2.2.1. Condition Optimization for Nickel-Catalyzed Oxidative Decarboxylative (Hetero)Arylation

We initially designed our reaction using 2-methyl-*N*-(quinolin-8-yl)benzamide (**1a**) and 4-methyl-2-phenyl-1,3-thiazole-5-carboxylate (**2a**) in the presence of a catalyst and oxidant. We began using a copper catalyst since copper salts have been shown to undergo a directed C–H arylation[39] and enable the decarboxylation of a broad scope of benzoic acids.[40] However, all attempts to use copper for this transformation were unsuccessful (Table 2.1 entry 1). Surprisingly, Ni salts were found to generate the desired ODC product in high yield when compared to copper (Table 2.1 entry 2). The use of $Ni(OAc)_2 \cdot 4H_2O$ was found to be the most effective pre-catalyst which generated the desired ODC product in 45% yield (Table 2.1 entry 3). We then found that using pivalic acid as an additive increased the yield from 45% to 64% (Table 2.1 entry 5). Finally,

when the loading of 4-methyl-2-phenyl-1,3-thiazole-5-carboxylate (**2a**) was lowered from 5 equiv to 3 equiv we were able to achieve quantitative yields of the desired ODC product. In contrast, when there is no nickel or silver present in the reaction, no desired product is formed (Table 2.1 entry 7 and 8). Therefore, our final optimized conditions consisted of 20 mol% of $Ni(OAc)_2•4H_2O$, Ag_2CO_3 (2.0 equiv), Na_2CO_3 (4.0 equiv), and PivOH (1.5 equiv) in DMA at 110 °C for 24 h. This finding was quite interesting because nickel salts have been shown to be effective catalyst for directed C–H activation.[41] However, their use in oxidative decarboxylative arylations have been shown in only two previous examples, both of which are limited to the reactions of 2-nitro- and pentafluorobenzoic acids with activated C–H bonds.[42]

Table 2.1. Optimization for oxidative decarboxylative (hetero)arylation[a]



entry	catalyst	oxidant	additive	yield (%)[b]
1	$Cu(OAc)_2$	Ag_2CO_3	-	17
2	$NiBr_2•H_2O$	Ag_2CO_3	-	29
3	$Ni(OAc)_2•4H_2O$	Ag_2CO_3	-	45
4	$Ni(OAc)_2•4H_2O$	AgOAc	-	11
5[c]	$Ni(OAc)_2•4H_2O$	Ag_2CO_3	PivOH	64
6[a]	**$Ni(OAc)_2•4H_2O$**	**Ag_2CO_3**	**PivOH**	**> 95 (93)**[e]
7[a]	-	Ag_2CO_3	PivOH	0
8[a]	$Ni(OAc)_2•4H_2O$	-	PivOH	0

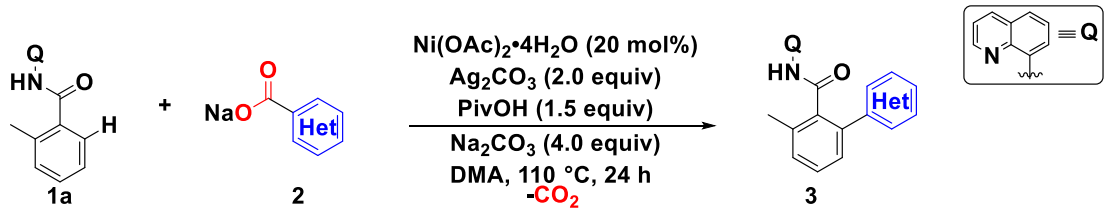
[a]Reaction conditions: Benzamide **1a** (0.2 mmol), heteroaromatic carboxylate **2a** (1.0 mmol) in DMA (2 mL). [b]^{1}H NMR yield with 1,3,5-trimethoxybenzene as an internal standard. [c]Pivalic acid (0.3 mmol) [d]Heteroaromatic carboxylate **2a** (0.6 mmol) [e]Isolated yield

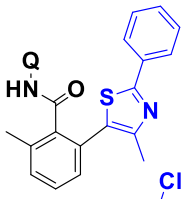
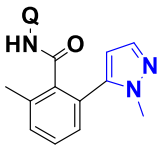
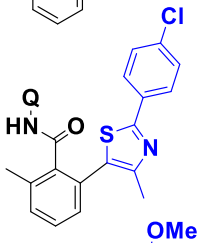
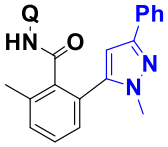
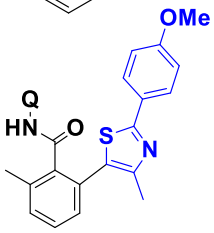
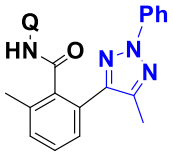
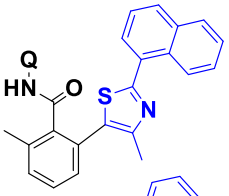
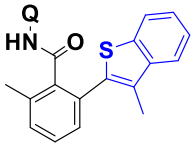
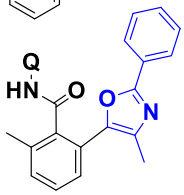
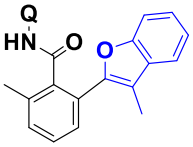
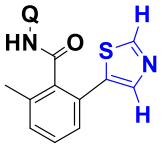
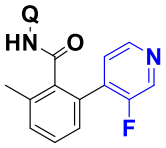
2.2.2. Exploration of the Nickel-Catalyzed Oxidative Decarboxylative (Hetero)Arylation Substrate Scope

Since heteroaromatic carboxylates were successfully coupled using this new Ni-catalyst system, we examined the scope of this new reactivity (Table 2.2). Thiazole derivatives

bearing electron-withdrawing groups (**3a**, **3b**, and **3d**) gave higher yields than those bearing electron-donating groups (**3c**). Not only do thiazole carboxylates undergo oxidative decarboxylative coupling but also oxazoles in 74% yield (**3e**). The unsubstituted thiazole-5-carboxylate (**3f**) also undergoes coupling with complete chemoselectivity at the C–5 position in 90% yield. We were encouraged to see this new method could also be extended to pyrazoles (**3g** and **3h**), triazole (**3i**), benzoazoles (**3j** and **3k**), and *ortho*-fluoro pyridine (**3l**).

Table 2.2. Heteroaromatic carboxylate scope of the nickel-catalyzed oxidative decarboxylative (hetero)arylation[a]

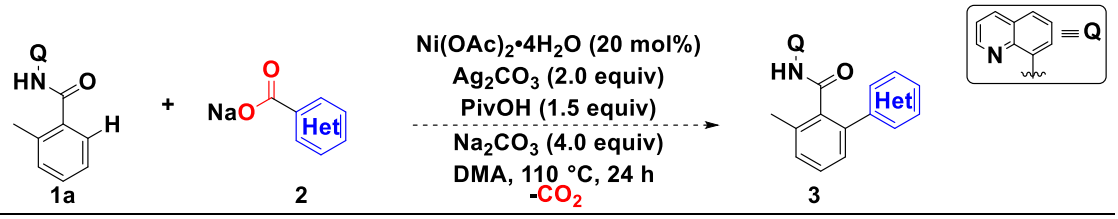


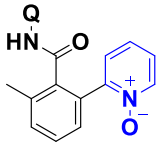
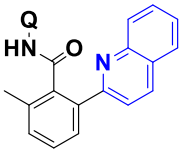
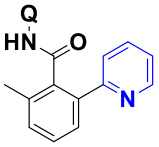
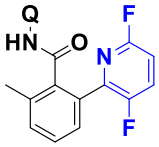
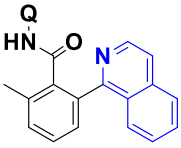
Entry			Entry		
1		3a, 93%	7		3g, 74%
2		3b, 89%	8		3h, 70%
3		3c, 72%	9		3i, 40%
4		3d, 93%	10		3j, 70%
5		3e, 74%	11		3k, 36%
6		3f, 90%	12		3l, 35%

[a]Isolated yields. Reaction conditions: Benzamide **1a** (0.2 mmol), heteroaromatic carboxylate **2** (0.6 mmol), $Ni(OAc)_2$•$4H_2O$ (20 mol %), Ag_2CO_3 (2.0 equiv), Na_2CO_3 (4.0 equiv), and PivOH (1.5 equiv) in DMA (2 mL) for 24 h at 110 °C under a N_2 atmosphere.

However, other pyridine carboxylates such as picolinic carboxylate, picolonic carboxylate *N*-oxide, and 1-isoquinoline carboxylate did not undergo decarboxylative coupling (Table 2.3). This could be due to the thermal instability of the pyridine derivatives, which are known to undergo thermal decarboxylation at lower temperature than our reaction conditions.[43] These data show pyridine derivatives with *ortho*-carboxylates were not able to undergo cross-coupling.

Table 2.3. Heteroaromatic carboxylates that do not undergo oxidative decarboxylative coupling[a, b]



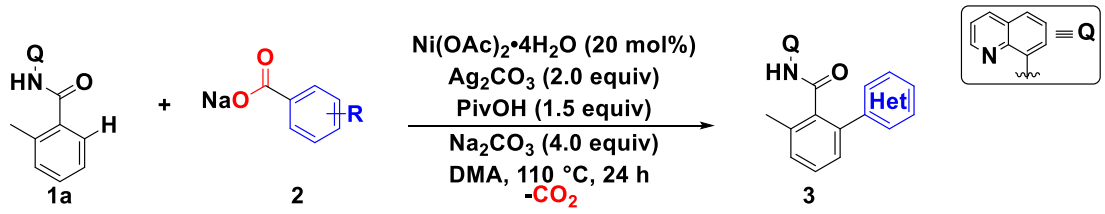
Entry			Entry		
1		3m, ND	5		3p, ND
2		3n, ND	6		3q, ND
3		3o, ND			

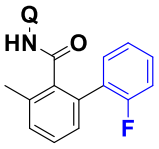
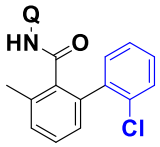
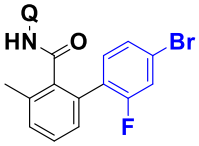
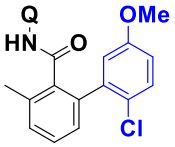
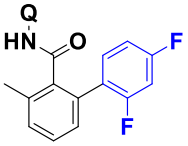
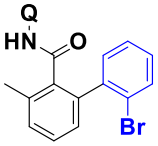
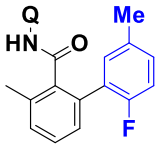
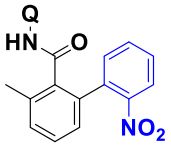
[a]Reaction conditions: Benzamide **1a** (0.2 mmol), heteroaromatic carboxylate **2** (0.6 mmol), $Ni(OAc)_2$•$4H_2O$ (20 mol %), Ag_2CO_3 (2.0 equiv), Na_2CO_3 (4.0 equiv), and PivOH (1.5 equiv) in DMA (2 mL) for 24 h at 110 °C under a N_2 atmosphere. [b]ND = None detected by ^1H NMR with 1,3,5-trimethoxybenzene as an internal standard.

Next, we wanted to demonstrate that our new Ni-catalyst system was not limited to only coupling heteroaromatic carboxylates. We then investigated the reactivity of benzoates under the optimized reaction conditions, (Table 2.4). Decarboxylative arylation of the *ortho*-substituted benzoates proceeded cleanly with electron-donating and electron-withdrawing substitutes in varying positions. As shown in Table 2.4, 2-fluorobenzoates

provided the highest yields (**3r**, **3s**, **3t**, and **3u**) over other *ortho*-substituted benzoates. It should be noted that arylbromides and chlorides are tolerated under these reaction conditions allowing for further functionalization.

Table 2.4. Benzoate scope of the nickel-catalyzed oxidative decarboxylative (hetero)arylation[a]



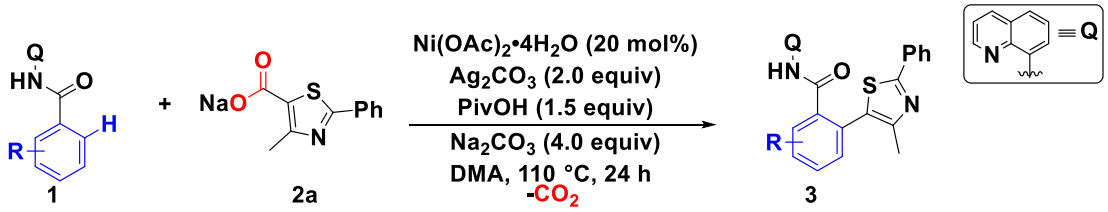
Entry			Entry		
1		3r, 70%	5		3v, 42%
2		3s, 58%	6		3w, 40%
3		3t, 55%	7		3x, 33%[b]
4		3u, 60%	8		3y, 28%[b]

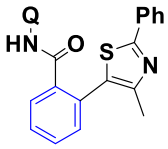
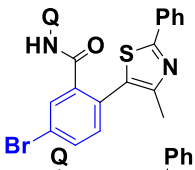
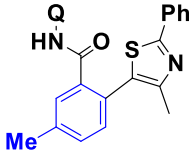
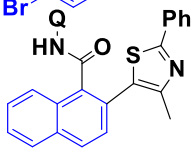
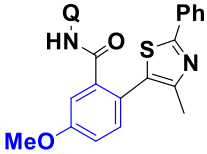
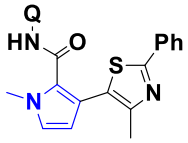
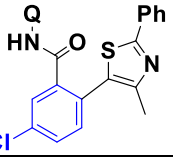
[a]Isolated yields. Reaction conditions: Benzamide **1a** (0.2 mmol), benzoate **2** (0.6 mmol), $Ni(OAc)_2•4H_2O$ (20 mol %), Ag_2CO_3 (2.0 equiv), Na_2CO_3 (4.0 equiv), and PivOH (1.5 equiv) in DMA (2 mL) for 24 h at 110 °C under a N_2 atmosphere. [b]^{1}H NMR yield with 1,3,5-trimethoxybenzene as an internal standard.

Lastly, we explored the scope of the substituted benzamides (Table 2.5). Benzamides with different substituents were explored first. When the unsubstituted benzamide is submitted to the standard reaction conditions, both mono- and diarylation products were formed. Benzamides with *meta*- substituents (**3aa – 3ad**) showed regioselective arylation at the less-hindered *ortho*-C–H bond. This new catalyst system again tolerates aryl

halides (**3ac** and **3ad**) as seen in Table 2.4. Other benzamides such as naphthyl (**3ae**) and *N*-methylpyrrole (**3af**) also undergo arylation in good yields.

Table 2.5. Benzamide scope of the nickel-catalyzed oxidative decarboxylative (hetero)arylation[a]



Entry			Entry		
1		3z, 45% (26% disubst)	5		3ad, 55%
2		3aa, 86%	6		3ae, 80%
3		3ab, 80%	7		3af, 74%
4		3ac, 61%			

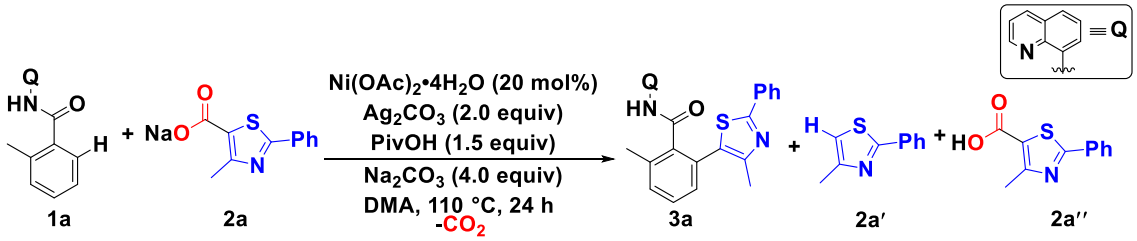
[a]Isolated yields. Reaction conditions: Benzamide **1** (0.2 mmol), heteroaromatic carboxylate **2a** (0.6 mmol), $Ni(OAc)_2$•$4H_2O$ (20 mol %), Ag_2CO_3 (2.0 equiv), Na_2CO_3 (4.0 equiv), and PivOH (1.5 equiv) in DMA (2 mL) for 24 h at 110 °C under a N_2 atmosphere.

2.2.3. Preliminary Mechanistic Experiments of the Nickel-Catalyzed Oxidative Decarboxylative (Hetero)Arylation

To gain insight into the reaction pathway of this new reaction, we conducted a series of experiments. As mentioned earlier in the optimization of the reaction conditions, when there is no nickel or silver present no product is formed (Table 2.6). When the standard reaction was conducted only in the presence of silver no product **3a** was formed, however, 85 % of the protodecarboxylated 4-methyl-2-phenyl-1,3-thiazole was recovered

(Table 2.6 entry 2). In contrast, when the experiment is conducted in the presence of only nickel there is quantitative recovery of the heteroaromatic carboxylic acid (**2a″**, entry 3). These data show that silver could be responsible for decarboxylation, while nickel is needed for the C–C bond formation.

Table 2.6. Control experiments of the nickel-catalyzed oxidative decarboxylative (hetero)arylation[a]

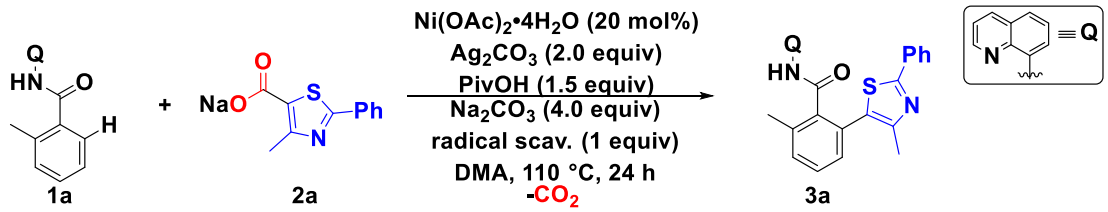


entry	catalyst	oxidant	yield (%)[b]	yield (%)[b]	yield (%)[b]
1	$Ni(OAc)_2 \cdot 4H_2O$	Ag_2CO_3	> **95**	65	0
2	-	Ag_2CO_3	0	**85**	0
3	$Ni(OAc)_2 \cdot 4H_2O$	-	0	0	> **95**

[a]Reaction conditions: Benzamide **1a** (0.2 mmol), heteroaromatic carboxylate **2a** (0.6 mmol), $Ni(OAc)_2$•$4H_2O$ (20 mol %), Ag_2CO_3 (2.0 equiv), Na_2CO_3 (4.0 equiv), and PivOH (1.5 equiv) in DMA (2 mL) for 24 h at 110 °C under a N_2 atmosphere. [b]^{1}H NMR yield with 1,3,5-trimethoxybenzene as an internal standard.

As previously mentioned in Chapter 1, it is known that silver salts can promote the decarboxylation of benzoic acids to generate silver-aryl or radical intermediates.[16] We first probed our reaction conditions with radical trapping reagents such as TEMPO and DHA (Table 2.7). In the presence of 1 equiv of either radical scavenger, there were no trappable radical intermediates and no decrease in the yield of the desired product **3a**. These data suggest there could be a silver-aryl intermediate that plays a key role in this reaction.

Table 2.7. Radical scavengers with the nickel-catalyzed oxidative decarboxylative (hetero)arylation [a]

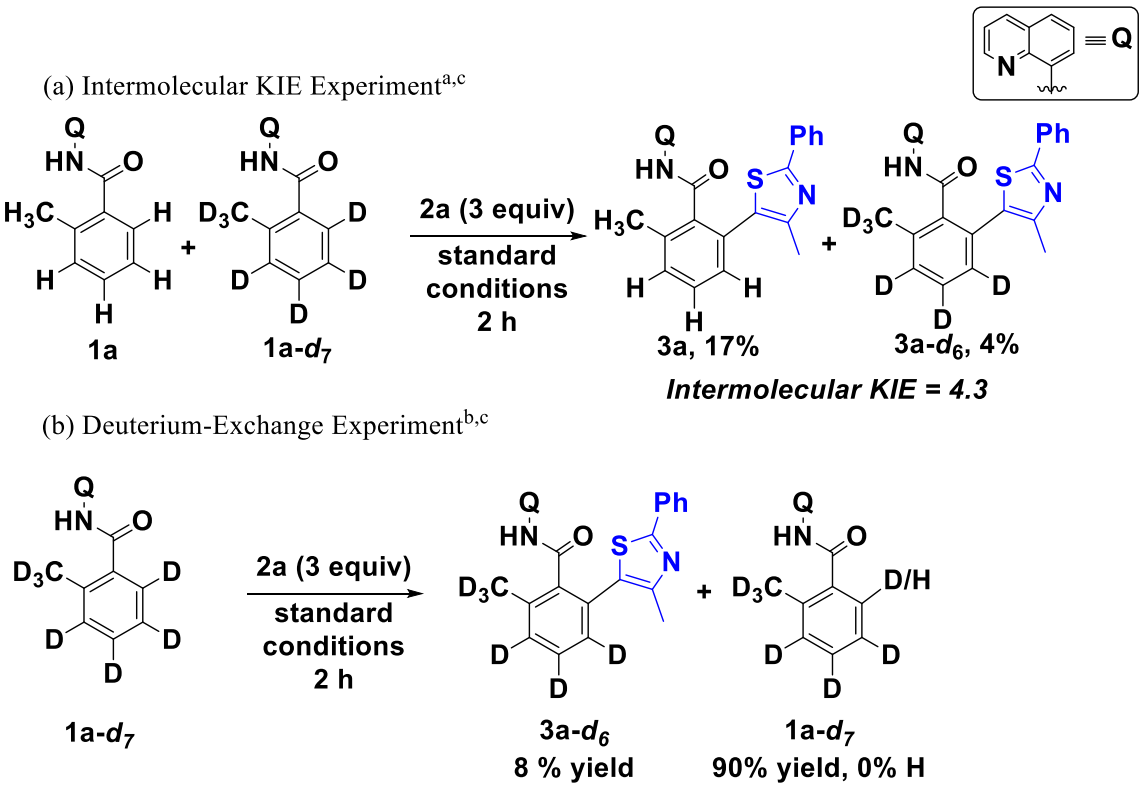


entry	Radical scav. (1 equiv)	yield (%)[b]
1	none	>95
2	TEMPO	>95
3	DHA	>95

[a]Reaction conditions: Benzamide **1a** (0.2 mmol), heteroaromatic carboxylate **2a** (0.6 mmol), $Ni(OAc)_2$•$4H_2O$ (20 mol %), Ag_2CO_3 (2.0 equiv), Na_2CO_3 (4.0 equiv), radical scavenger (1.0 equiv) and PivOH (1.5 equiv) in DMA (2 mL) for 24 h at 110 °C under a N_2 atmosphere. [b]^{1}H NMR yield with 1,3,5-trimethoxybenzene as an internal standard.

Next, we explored the C–H activation step of our new reaction method. The kinetic isotope effect obtained from the intermolecular competition (Scheme 15a) experiment reveled k_H/k_D = 4.3. The deuterium-exchange of **1a-*d*$_7$** under our standard reaction conditions showed no proton incorporation of the *ortho*-C–D bond in the recovered starting material (Scheme 15b) by ^{1}H NMR spectroscopy. These data suggest that the C–H activation step is irreversible and consistent with a primary isotope effect.[44] If this is the case, we might be able to isolate a stable nickel metallacycle; this will be discussed later in Chapter 4.

Scheme 15. Kinetic isotope effect of the nickel-catalyzed oxidative decarboxylative (hetero)arylation.[a]



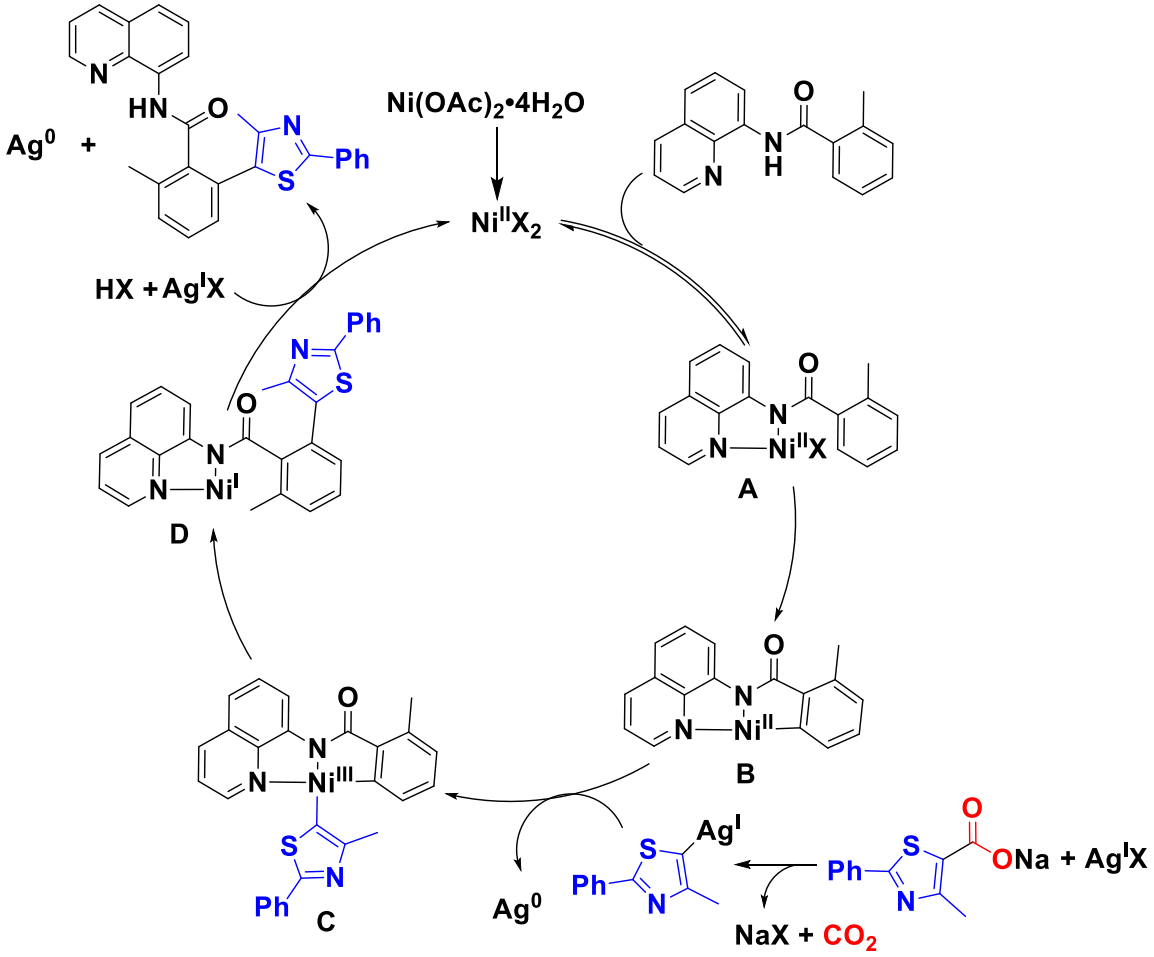
[a]Reaction conditions: Benzamide **1a** (0.1 mmol), **1a-*d*$_7$** (0.1 mmol), heteroaromatic carboxylate **2a** (0.6 mmol), $Ni(OAc)_2$•$4H_2O$ (20 mol %), Ag_2CO_3 (2.0 equiv), Na_2CO_3 (4.0 equiv), and PivOH (1.5 equiv) in DMA (2 mL) for 2 h at 110 °C under a N_2 atmosphere. [b]Benzamide **1a-*d*$_7$** (0.2 mmol), Heteroaromatic carboxylate **2a** (0.6 mmol), $Ni(OAc)_2$•$4H_2O$ (20 mol %), Ag_2CO_3 (2.0 equiv), Na_2CO_3 (4.0 equiv), and PivOH (1.5 equiv) in DMA (2 mL) for 2 h at 110 °C under a N_2 atmosphere. [c]^{1}H NMR yield with 1,3,5-trimethoxybenzene as an internal standard.

2.2.4. Proposed Reaction Mechanism of the Nickel-Catalyzed Oxidative Decarboxylative (Hetero)Arylation Reaction

From the results of the control experiments and kinetic isotope effect experiments mentioned above, we have proposed a mechanism for our new catalytic reaction (Scheme 16). The pre-catalyst enters the reaction pathway and becomes the active catalyst followed by ligand exchange with the amide **A** and then forming the nickel(II) metallacycle **B**. During this time, silver(I) carboxylate is formed and undergoes decarboxylation to form a silver(I)-aryl. The silver(I)-aryl undergoes transmetallation

with nickel complex **B** along with concomitant oxidation to form the nickel(III) metallacycle **C**. Reductive elimination from intermediate **C** generates the new C–C bond to form **D**. Intermediate **D** undergoes protonation and reoxidation of nickel(I) to close the catalytic cycle. We believe the remarkable efficiency of this new catalyst system is due to the cooperation of both nickel and silver together.

Scheme 16. Proposed reaction mechanism of the nickel-catalyzed oxidative decarboxylative (hetero)arylation.



2.3. Conclusion

In summary, we have developed the first nickel-catalyzed oxidative decarboxylative (hetero)arylation of unactivated C–H bonds. This method employs the use of $Ni(OAc)_2•4H_2O$ as the catalyst, Ag_2CO_3 as the oxidant, Na_2CO_3 as the base and PivOH as an additive to enable the efficient coupling of a broad scope of heteroaromatic carboxylates and *ortho*-substituted benzoates. The data from our control experiments show there could be cooperation between both nickel and silver. Silver could be responsible for decarboxylation and generation of a silver(I)-aryl, while nickel is needed for formation of the C–C bond.

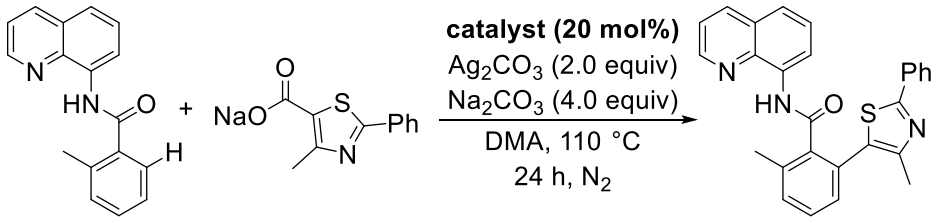
2.4. Experimental

General Information. All manipulations were performed using standard Schlenk or glovebox techniques under a nitrogen atmosphere. All solvents (including dry DMA) were bought from Alfa-Aesar, Fisher, and Cambridge Isotope and used as received. All other reagents were purchased from Maybridge, Oakwood, Acros, Alfa-Aesar, Astatech, Strem and CDN Isotopes and used without further purification. All NMR spectra were recorded at ambient temperature using Agilent 400 MHz (^{1}H, 400 MHz; ^{13}C{^{1}H}, 100 MHz; ^{19}F, 376 MHz) spectrometer. Chemical shifts are referenced to the residual solvent signals ($CDCl_3$, ^{1}H: 7.26 ppm, ^{13}C: 77.2 ppm) and (DMSO-d_6, ^{1}H: 2.50 ppm, ^{13}C: 39.5 ppm).[45] High resolution mass spectra were obtained on a Thermo Finnigan Linear Trapping Quadrupole mass spectrometer. IR spectra were recorded on a PerkinElmer (Spectrum 100) FT-IR spectrometer. Column chromatography was performed using Silicycle Silia Flash P60 silica gel.

General Procedure for the Optimization of the Oxidative Decarboxylative Arylation Reaction. An oven-dried 50 mL Schlenk tube with a stirring bar was charged with 4-methy-2-phenyl-1,3-thiazole-5-carboxylic acid **2a** (131 mg, 0.600 mmol), sodium carbonate (63 mg, 0.60 mmol), and dry DMA (1 mL). The reaction vessel was placed in a pre-heated oil bath and stirred for 0.5 h at 130 °C. The solvent was removed under reduced pressure until dry and the carboxylate salt was used without further purification. 2-methyl-N-(quinolin-8-yl) benzamide **1a** (52.4 mg, 0.200 mmol), $Ni(OAc)_2•4H_2O$ (9.9

mg, 0.040 mmol), Ag_2CO_3 (110 mg, 0.400 mmol), Na_2CO_3 (83 mg, 0.80 mmol), and PivOH (30.6 mg, 0.300 mmol) were added and the tube was evacuated and backfilled with nitrogen three times after which DMA (2 mL) was added *via* syringe. The reaction mixture was stirred at 110 °C for 24 h. Upon completion, the reaction tube was cooled to room temperature. The solution was diluted with ethyl acetate (25 mL) and poured into a 250 mL separatory funnel. To the solution, water (25 mL), Na_2EDTA (500 mg), aqueous HCl (1N, 10 mL) were added and extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with water (100 mL) and brine (25 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. Then 1,3,5-trimethoxybenzene (5.00 mg) was added to the residue and the crude mixture was dissolved in $CDCl_3$ for ^1H analysis.

Optimization of the Pre-catalyst[a]

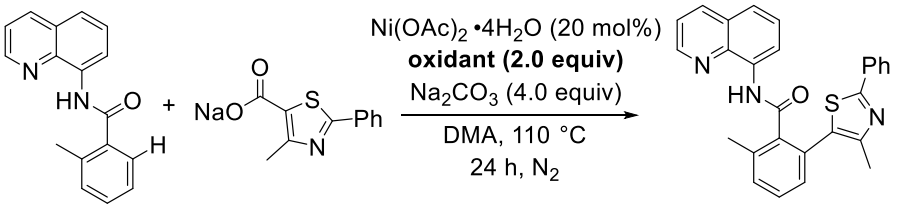


1a **2a** **3a**

entry	catalyst	yield **3a** (%)[b]
1	$Ni(OAc)_2•4H_2O$	45
2	$Cu(OAc)_2$	17
3	$Ni(HCO_2)_2•2H_2O$	15
4	$NiBr_2•H_2O$	29
5	$Ni(acac)_2$	19
6	$NiCl_2$	15
7	NiI_2	32
8	$Ni(OTf)_2$	21
9[c]	$Ni(OAc)_2•4H_2O$	8

[a]Reaction conditions: **1a** (0.200 mmol), **2a** (1.00 mmol) in solvent (2 mL). [b]^1H NMR yield with 1,3,5-trimethoxybenzene as an internal standard. [c]10 mol%

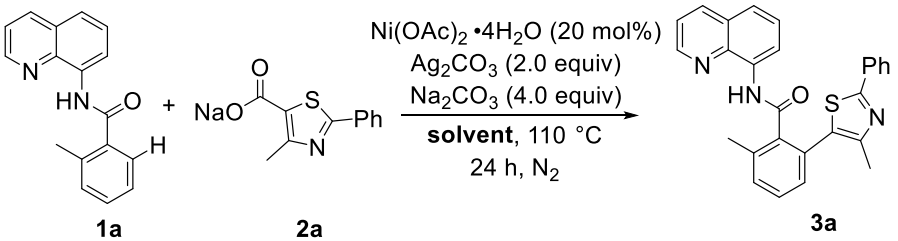
Optimization of the Oxidant[a]



entry	oxidant	yield **3a** (%)[b]
1	Ag_2CO_3	45
2	$AgNO_3$	16
3	AgOAc	11
4	AgOTf	19
5	Ag_2O	9
6	O_2	0

[a]Reaction conditions: **1a** (0.200 mmol), **2a** (1.00 mmol) in solvent (2 mL). [b]^{1}H NMR yield with 1,3,5-trimethoxybenzene as an internal standard.

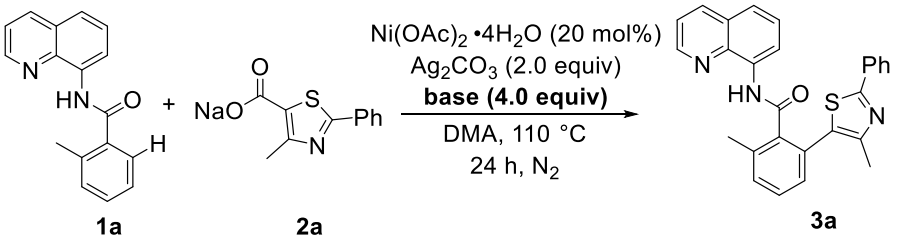
Optimization of the Solvent[a]



entry	solvent	yield **3a** (%)[b]
1	DMA	45
2	DMF	13
3	NMP	35
4	Diglyme	0
5	$PhCH_3$	0

[a]Reaction conditions: **1a** (0.200 mmol), **2a** (1.00 mmol) in solvent (2 mL). [b]^{1}H NMR yield with 1,3,5-trimethoxybenzene as an internal standard.

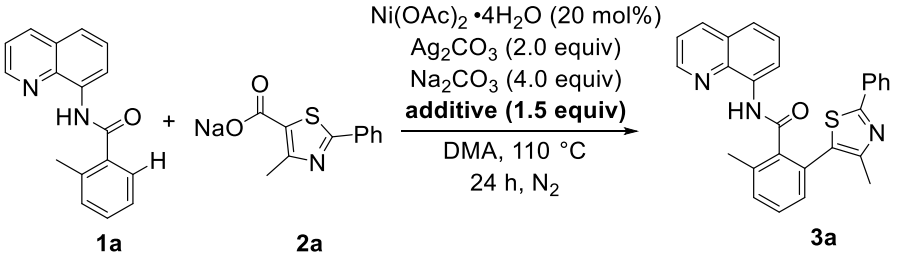
Optimization of the Base[a]



entry	[base]	yield **3a** (%)[b]
1	Na_2CO_3	45
2	Li_2CO_3	20
3	K_2CO_3	0
4	NaOAc	25
5	pyridine	15

[a]Reaction conditions: **1a** (0.200 mmol), **2a** (1.00 mmol) in solvent (2 mL). [b]^{1}H NMR yield with 1,3,5-trimethoxybenzene as an internal standard.

Optimization of the Additives[a]



entry	[additive]	yield **3a** (%)[b]
1	Pivalic Acid	64
2	Acetic Acid	42
3	Trifluoroacetic acid	34

[a]Reaction conditions: **1a** (0.200 mmol), **2a** (1.00 mmol) in solvent (2 mL). [b]^{1}H NMR yield with 1,3,5-trimethoxybenzene as an internal standard.

General Procedure for the Ni–Catalyzed Oxidative Decarboxylative Arylation. Procedure A (Generation of Sodium Salts at 130 °C): An oven-dried 50 mL Schlenk tube with a stirring bar was charged with carboxylic acid **2** (0.600 mmol), Na_2CO_3 (63 mg, 0.60 mmol), and dry DMA (1 mL). The reaction vessel was placed in a pre-heated oil bath and stirred for 0.5 h at 130 °C. The solvent was removed under reduced pressure until dry and the carboxylate salt was used without further purification. *N*-(quinolin-8-yl)

benzamide **1** (0.200 mmol), $Ni(OAc)_2 \cdot 4H_2O$ (9.9 mg, 0.040 mmol), Ag_2CO_3 (110 mg, 0.400 mmol), Na_2CO_3 (83 mg, 0.80 mmol), and PivOH (30.6 mg, 0.300 mmol) were added and the tube was evacuated and backfilled with nitrogen three times after which DMA (2 mL) was added *via* syringe. The reaction mixture was stirred at 110 °C for 24 h. Upon completion, the reaction tube was cooled to room temperature. The solution was diluted with ethyl acetate (25 mL) and poured into a 250 mL separatory funnel. To the solution, water (25 mL), Na_2EDTA (500 mg), aqueous HCl (1N, 10 mL) were added and the mixture was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with water (100 mL) and brine (25 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography (gradient elution, hexanes : ethyl acetate (19:1, v/v) to (1:1, v/v)), to yield the corresponding product.

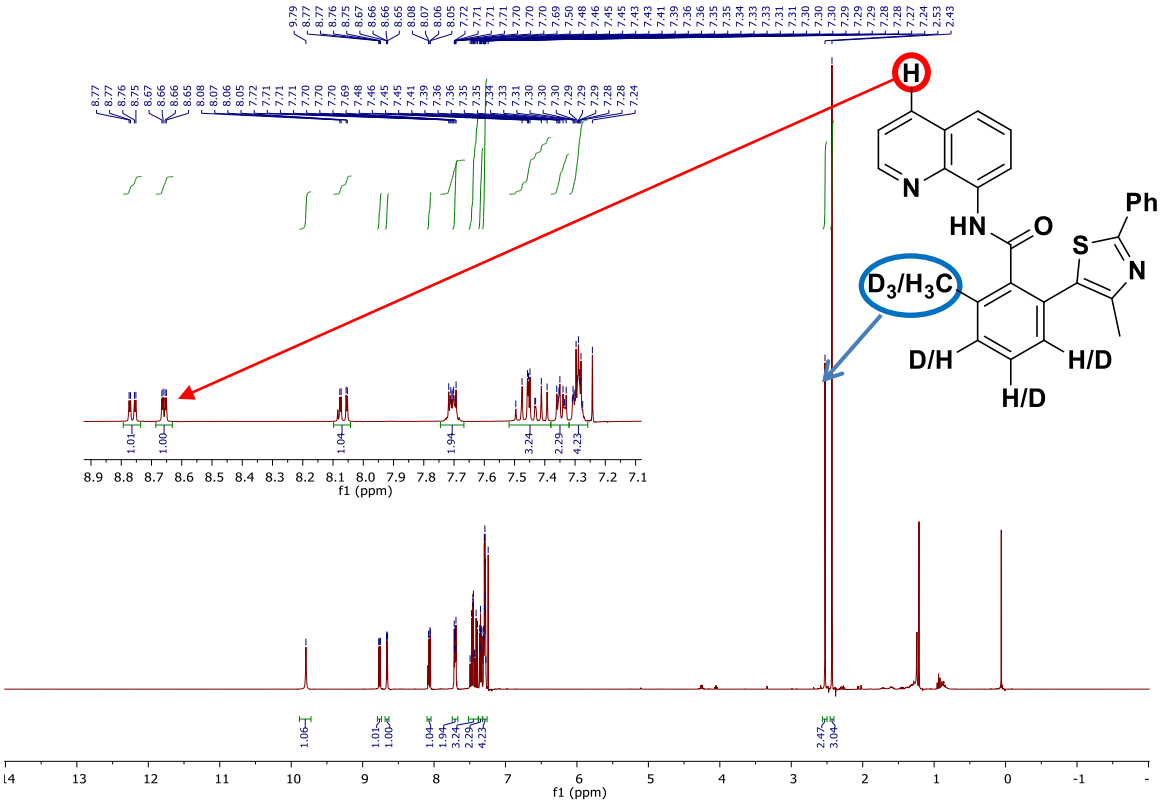
Procedure B (Generation of Sodium Salts at 110 °C): An oven-dried 50 mL Schlenk tube with a stirring bar was charged with carboxylic acid **2** (0.600 mmol), Na_2CO_3 (63 mg, 0.60 mmol), and dry DMA (1 mL). The reaction vessel was placed in a pre-heated oil bath and stirred for 0.5 h at 110 °C. The solvent was removed under reduced pressure until dry and the carboxylate salt was used without further purification. *N*-(quinolin-8-yl) benzamide **1** (0.200 mmol), $Ni(OAc)_2 \cdot 4H_2O$ (9.9 mg, 0.040 mmol), Ag_2CO_3 (110 mg, 0.400 mmol), Na_2CO_3 (83 mg, 0.80 mmol), and PivOH (30.6 mg, 0.300 mmol) were added and the tube was evacuated and backfilled with nitrogen three times after which DMA (2 mL) was added *via* syringe. The reaction mixture was stirred at 110 °C for 24 h. Upon completion, the reaction tube was cooled to room temperature. The solution was diluted with ethyl acetate (25 mL) and poured into a 250 mL separatory funnel. To the solution, water (25 mL), Na_2EDTA (500 mg), aqueous HCl (1N, 10 mL) were added and the mixture was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with water (100 mL) and brine (25 mL), dried Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (gradient elution, hexanes:ethyl acetate (19:1, v/v) to (1:1, v/v)), yielding the corresponding product.

Reactions with Radical Scavengers.

An oven-dried 50 mL Schlenk tube with a stirring bar was charged with 4-methy-2-phenyl-1,3-thiazole-5-carboxylic acid **2a** (131 mg, 0.600 mmol), sodium carbonate (63 mg, 0.60 mmol), and dry DMA (1 mL). The reaction vessel was placed in a pre-heated oil bath and stirred for 0.5 h at 130 °C. The solvent was removed under reduced pressure until dry and the resulting carboxylate salt was used without further purification. 2-methyl-N-(quinolin-8-yl) benzamide **1a** (52.4 mg, 0.200 mmol), $Ni(OAc)_2$•$4H_2O$ (9.9 mg, 0.040 mmol), Ag_2CO_3 (110 mg, 0.400 mmol), Na_2CO_3 (83 mg, 0.80 mmol), TEMPO (31.2 mg, 0.200 mmol) or DHA (36.0, 0.200 mmol), and PivOH (30.6 mg, 0.300 mmol) were added and the tube was evacuated and backfilled with nitrogen three times after which DMA (2 mL) was added *via* syringe. The reaction mixture was stirred at 110 °C for 24 h. Upon completion, the reaction tube was cooled to room temperature. The solution was diluted with ethyl acetate (25 mL) and poured into a 250 mL separatory funnel. To the solution, water (25 mL), Na_2EDTA (500 mg), aqueous HCl (1N, 10 mL) were added and extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with water (100 mL) and brine (25 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. Then 1,3,5-trimethoxybenzene (5.00 mg) was added to the residue and the crude mixture was dissolved in $CDCl_3$ for ^1H analysis.

Procedure for the Intermolecular Competition Experiment. An oven-dried 50 mL Schlenk tube with a stirring bar was charged with carboxylic acid **2** (0.600 mmol), sodium carbonate (63 mg, 0.60 mmol), and dry DMA (1 mL). The reaction vessel was placed in a pre-heated oil bath and stirred for 0.5 h at 130 °C. Solvent was removed under reduced pressure until dry and the resulting carboxylate salt was used without further purification. **1a** (26.2 mg, 0.100 mmol), **1a-*d*$_7$** (26.9 mg, 0.100 mmol), $Ni(OAc)_2$•$4H_2O$ (9.9 mg, 0.040 mmol), Ag_2CO_3 (110 mg, 0.400 mmol), Na_2CO_3 (83 mg, 0.80 mmol), PivOH (30.6 mg, 0.300 mmol) were added, the tube was evacuated and backfilled with nitrogen three times after which DMA (2 mL) was added *via* syringe. The reaction mixture was stirred at 110 °C for 2 h. Upon completion, the reaction tube was cooled to

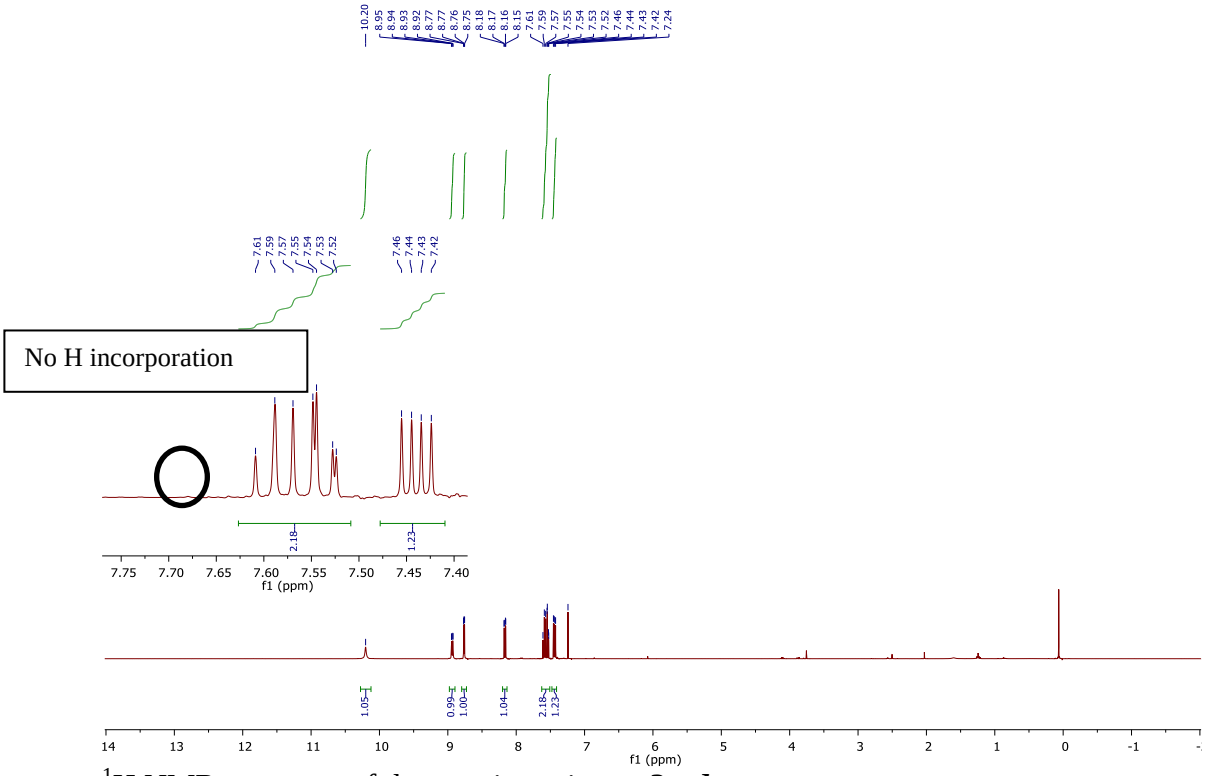
room temperature. The solution was diluted with ethyl acetate (25 mL) and poured into a 250 mL separatory funnel. To the solution, water (25 mL), Na_2EDTA (500 mg), aqueous HCl (1N, 10 mL) were added and extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with water (100 mL) and brine (25 mL), dried Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (gradient elution, hexanes:ethyl acetate (19:1, v/v) to (4:1, v/v)), yielding the corresponding product of **3a** and **3a-*d*$_6$** in 17% and 4% yields respectively, giving a KIE of 4.3 by ^{1}H NMR spectroscopy.



^{1}H NMR spectrum of the reaction mixture of **3a** and **3a-*d*$_6$**

Procedure for the Isotopic Exchange Experiment. An oven-dried 50 mL Schlenk tube with a stirring bar was charged with carboxylic acid **2** (0.600 mmol), sodium carbonate (63 mg, 0.60 mmol), and dry DMA (1 mL). The reaction vessel was placed in a pre-heated oil bath and stirred for 0.5 h at 130 °C. Solvent was removed under reduced pressure until dry and the resulting carboxylate salt was used without further purification.

1a-*d*$_7$ (53.8 mg, 0.200 mmol), $Ni(OAc)_2$•$4H_2O$ (9.9 mg, 0.040 mmol), Ag_2CO_3 (110 mg, 0.400 mmol), Na_2CO_3 (83 mg, 0.80 mmol), PivOH (30.6 mg, 0.300 mmol) were added, the tube was evacuated and backfilled with nitrogen three times after which DMA (2 mL) was added *via* syringe. The reaction mixture was stirred at 110 °C for 2 h. Upon completion, the reaction tube was cooled to room temperature. The solution was diluted with ethyl acetate (25 mL) and poured into a 250 mL separatory funnel. To the solution, water (25 mL), Na_2EDTA (500 mg), aqueous HCl (1N, 10 mL) were added and extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with water and brine, dried Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (gradient elution, hexanes:ethyl acetate (19:1, v/v) to (4:1, v/v)), yielding the corresponding product. The extent of proton incorporation was determined by ^{1}H NMR spectroscopy.



^{1}H NMR spectrum of the reaction mixture **3a-*d*$_6$**

General Procedure for the Synthesis of (Hetero)Aryl Benzamides (1)

Procedure A: Synthesis from the benzoyl chloride. A 100 mL two-neck round bottom flask was charged with 8-aminoquinoline (1.44 g, 10.0 mmol), Et_3N (1.56 mL, 12.0 mmol), and methylene chloride (20 mL) under a N_2 atmosphere. The corresponding acid chloride was added dropwise at room temperature over 10 minutes. The mixture was stirred for 6 h at room temperature. The reaction was quenched with 10 mL of saturated $NaHCO_3$ and extracted with methylene chloride (3 x 25 mL). The combined organic layer was washed with brine (15 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified via silica gel column chromatography (gradient elution, hexanes : ethyl acetate (19:1, v/v) to (4:1, v/v)).

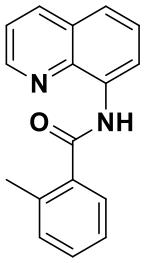
Procedure B: Synthesis from the carboxylic acid. A 50 mL two-neck round bottom flask was charged with the corresponding carboxylic acid (1.70 mmol), *N*,*N*-dimethylformamide (2 drops), and methylene chloride (2 mL) under a N_2 atmosphere at 0 °C. Oxalyl chloride (0.17 mL, 2.0 mmol) was then added dropwise and the reaction mixture was allowed to stir for 3 h at room temperature. The solvent was removed under reduced pressure and the acid chloride was used without further purification. A 100 mL two-neck round bottom flask was charged with 8-aminoquinoline (255 mg, 1.70 mmol), Et_3N (0.278 mL, 2.00 mmol), and methylene chloride (10 mL) under q N_2 atmosphere at 0 °C. The corresponding acid chloride was added dropwise to the reaction and stirred for 3 h. The reaction was quenched with 5 mL of saturated $NaHCO_3$ and extracted with methylene chloride three times (3 x 25 mL). The combined organic layer was washed with brine (15 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified via silica gel column chromatography (gradient elution, hexanes : ethyl acetate (19:1, v/v) to (9:1, v/v)).

General Procedure for the Synthesis of Thiazole Carboxylic Acids (2)

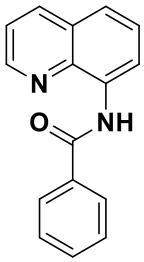
A mixture of thiobenzamide (3.77 g, 27.5 mmol) and ethyl 2-chloroacetoacetate (3.45 mL, 25.0 mmol) in methanol was refluxed for 5-6 h in a 100 mL round bottom flask. The

solvent was removed under reduced pressure to yield the corresponding crude ethyl carboxylate. A 250 mL round bottom flask was charged with the crude ethyl carboxylate, THF/EtOH/H_2O (1:1:1, 165 mL, v/v), and KOH (4 equiv) and the mixture was allowed to stir at room temperature overnight. The reaction was quenched with HCl (2 N) until a pH of 2 was reached. The solid was filtered and dried under reduced pressure to yield the corresponding carboxylic acid.

Characterization of (Hetero)Aryl Benzamides (1)

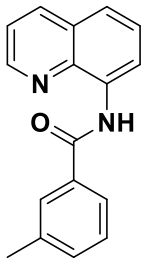


2-methyl-*N*-(quinolin-8-yl) benzamide (1a): The following compound was synthesized following General Procedure A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.95 (dd, *J* = 7.5, 1.5 Hz, 1H), 8.78 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.69 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.64 – 7.53 (m, 2H), 7.50 – 7.37 (m, 3H), 7.33 (tt, *J* = 7.7, 0.8 Hz, 2H), 2.61 (s, 3H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.17, 148.28, 138.60, 136.70, 136.64, 136.35, 134.76, 131.41, 130.36, 128.00, 127.40, 127.27, 126.05, 121.81, 121.69, 116.49, 20.27. The spectral data are consistent with those reported in the literature.[46]

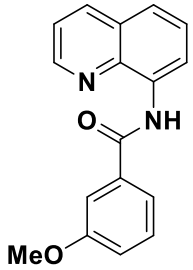


***N*-(quinolin-8-yl) benzamide (1z):** The following compound was synthesized following General Procedure A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.73 (s, 1H), 8.95 (dd, *J* = 7.5, 1.4 Hz, 1H), 8.82 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.12 – 8.06 (m, 2H), 7.62 – 7.48 (m, 5H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.47, 148.33, 138.81, 136.43, 135.21, 134.64, 131.90, 128.86, 128.04,

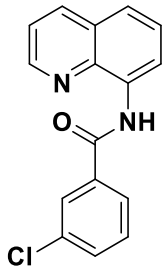
127.49, 127.35, 121.76, 121.74, 116.59. The spectral data are consistent with those reported in the literature.[46]



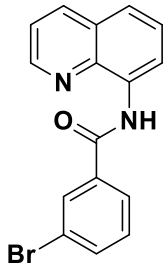
3-methyl-*N*-(quinolin-8-yl) benzamide (1aa): The following compound was synthesized following General Procedure A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.67 (s, 1H), 8.94 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.79 (dd, *J* = 4.2, 3.7, 1.7 Hz, 1H), 8.08 (dd, *J* = 8.2, 4.5, 1.7 Hz, 1H), 7.90 – 7.82 (m, 2H), 7.54 (td, *J* = 7.9, 2.8 Hz, 1H), 7.46 (ddd, *J* = 8.3, 3.5, 1.4 Hz, 1H), 7.44 – 7.32 (m, 3H), 2.45 (d, *J* = 2.3 Hz, 3H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.50, 148.19, 138.66, 138.58, 136.26, 135.07, 134.57, 132.55, 128.59, 127.99, 127.89, 127.33, 124.16, 121.59, 116.43, 21.45. The spectral data are consistent with those reported in the literature.[47]



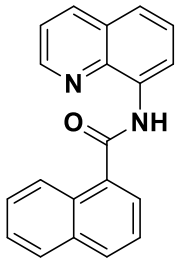
3-methoxy-*N*-(quinolin-8-yl) benzamide (1ab): The following compound was synthesized following General Procedure A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.73 (s, 1H), 8.93 (dd, *J* = 7.5, 1.1 Hz, 1H), 8.83 (dd, *J* = 4.2, 2.1 Hz, 1H), 8.16 (dd, 1H), 7.64 (tdd, *J* = 3.3, 1.7, 1.0 Hz, 2H), 7.62 – 7.56 (m, 1H), 7.56 – 7.51 (m, 1H), 7.50 – 7.41 (m, 2H), 7.12 (dd, *J* = 8.2, 2.5, 1.0 Hz, 1H), 3.91 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.08, 159.96, 148.26, 148.24, 138.63, 136.54, 136.29, 136.26, 134.48, 129.74, 127.89, 127.35, 127.31, 121.69, 121.64, 119.01, 118.99, 117.90, 117.84, 116.45, 116.41, 112.72, 112.71, 55.43. The spectral data are consistent with those reported in the literature.[48]



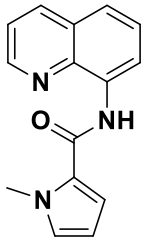
3-chloro-*N*-(quinolin-8-yl) benzamide (1ac): The following compound was synthesized following General Procedure A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.67 (s, 1H), 8.89 (dd, *J* = 7.3, 1.8 Hz, 1H), 8.83 (dd, *J* = 4.1, 2.0 Hz, 1H), 8.16 (dd, *J* = 8.3, 3.5, 1.6 Hz, 1H), 8.05 (d, *J* = 2.0 Hz, 1H), 7.93 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.61 – 7.50 (m, 3H), 7.46 (td, *J* = 7.4, 2.8 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.08, 147.93, 138.12, 136.33, 135.88, 134.59, 133.75, 131.40, 129.63, 127.46, 127.34, 126.85, 124.71, 121.63, 121.35, 116.17. The spectral data are consistent with those reported in the literature.[47]



3-bromo-*N*-(quinolin-8-yl) benzamide (1ad): The following compound was synthesized following General Procedure A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.60 (s, 1H), 8.84 (dd, *J* = 7.4, 1.6 Hz, 1H), 8.78 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.16 (t, *J* = 1.8 Hz, 1H), 8.09 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.92 (ddd, *J* = 7.8, 1.7, 1.0 Hz, 1H), 7.63 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.56 – 7.43 (m, 2H), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.72, 148.38, 138.65, 137.06, 136.38, 134.77, 134.21, 130.64, 130.29, 127.94, 127.36, 125.65, 123.07, 122.03, 121.77, 116.67. The spectral data are consistent with those reported in the literature.[47]

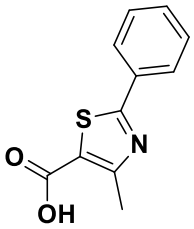


***N*-(quinolin-8-yl)naphthalene-1-carboxamide (1ae):** The following compound was synthesized following General Procedure A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 9.09 (dd, *J* = 7.7, 1.3 Hz, 1H), 8.74 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.61 – 8.55 (m, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.00 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.93 (ddd, *J* = 7.3, 5.5, 1.6 Hz, 2H), 7.65 (t, *J* = 7.9 Hz, 1H), 7.63 – 7.53 (m, 4H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.78, 148.37, 138.68, 136.41, 134.90, 133.96, 131.21, 130.43, 128.47, 128.08, 127.49, 127.39, 127.38, 126.59, 125.66, 125.59, 124.94, 122.03, 121.76, 116.78. The spectral data are consistent with those reported in the literature.[47]

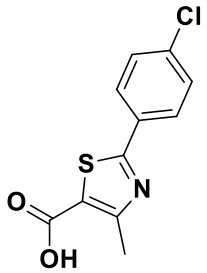


1-methyl-N-(quinolin-8-yl)-1H-pyrrole-2-carboxamide (1af): The following compound was synthesized following General Procedure B. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.43 (s, 1H), 8.86 – 8.74 (m, 2H), 8.13 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.55 (t, *J* = 7.9 Hz, 1H), 7.47 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.43 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.02 (dd, *J* = 4.0, 1.7 Hz, 1H), 6.81 (t, *J* = 2.1 Hz, 1H), 6.21 (dd, *J* = 4.0, 2.5 Hz, 1H), 4.06 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.11, 148.21, 138.65, 136.34, 135.13, 128.90, 127.47, 126.34, 121.65, 121.00, 115.86, 115.85, 113.09, 107.67, 37.03. The spectral data are consistent with those reported in the literature.[47]

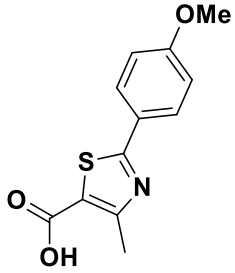
Characterization of Thizaole Carboxylic Acids (2).



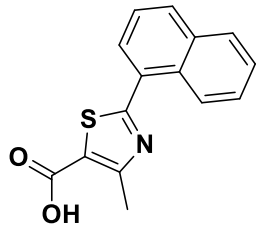
4-methyl-2-phenyl-1,3-thiazole-5-carboxylic acid (2a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.30 (s, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.63 – 7.39 (m, 3H), 2.67 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 168.44, 162.92, 159.61, 132.36, 131.18, 129.29, 126.47, 122.91, 17.14. The spectral data are consistent with those reported in the literature.[49]



2-(4-chlorophenyl)-4-methyl-1,3-thiazole-5-carboxylic acid (2b). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.42 (s, 1H), 7.94 (d, J = 8.6 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H), 2.66 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 166.86, 162.70, 159.51, 135.73, 131.04, 129.15, 127.94, 123.23, 16.96. The spectral data are consistent with those reported in the literature.[49]

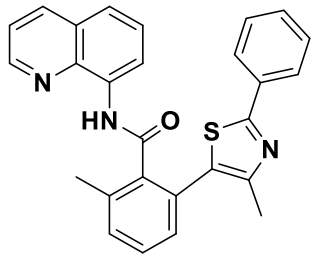


2-(4-methoxyphenyl)-4-methyl-1,3-thiazole-5-carboxylic acid (2c). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.26 (s, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 8.6 Hz, 2H), 3.83 (s, 3H), 2.64 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 168.44, 163.07, 161.63, 159.61, 128.14, 125.16, 121.69, 114.56, 55.40, 17.13. The spectral data are consistent with those reported in the literature.[50]



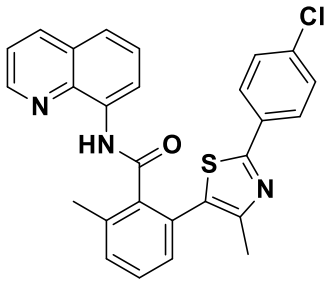
4-methyl-2-(naphthalene-1-yl)-1,3-thiazole-5-carboxylic acid (2d): White solid, mp = 207 – 209 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.44 (s, 1H), 8.81 (d, 1H), 8.08 (dd, *J* = 8.4, 2.1, 1.0 Hz, 1H), 8.01 (d, 1H), 7.90 (dt, *J* = 7.2, 1.7 Hz, 1H), 7.66 – 7.55 (m, 3H), 2.76 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 168.48, 163.05, 159.35, 133.67, 131.22, 129.62, 129.36, 128.92, 128.53, 127.62, 126.56, 125.49, 125.34, 123.60, 17.32. FTIR (ATR, cm^{-1}): 3330, 3156, 1690, 1614, 1421, 1258, 911. HRMS (ESI-MS) m/z calcd for $C_{15}H_{12}NO_2S$ $[M + H]^+$ 270.0589 found 270.0595.

Characterization of Ni-Catalyzed Oxidative Decarboxylative (Hetero) Arylation Products.

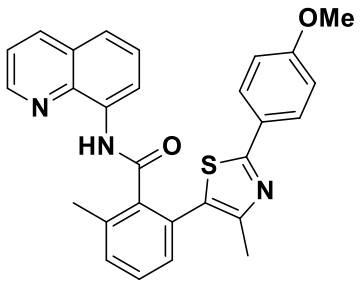


2-methyl-6-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-*N*-(quinolin-8-yl)benzamide (3a): The title compound was synthesized following General Procedure A. Light yellow solid in 93 % (81.0 mg, 0.18 mmol), mp = 146 – 148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.83 (s, 1H), 8.80 (dd, *J* = 7.3, 1.7 Hz, 1H), 8.67 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.05 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.77 – 7.69 (m, 2H), 7.52 – 7.39 (m, 3H), 7.39 – 7.27 (m, 6H), 2.55 (s, 3H), 2.46 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.11, 166.18, 150.90, 148.02, 138.68, 138.30, 136.18, 134.14, 133.45, 130.89, 129.63, 129.20, 129.18, 129.17, 129.02, 128.65, 127.84, 127.23, 126.23, 121.91, 121.52, 116.59, 19.82, 15.97. FTIR (ATR, cm^{-1}):

3339, 3061, 2921, 1670, 1580, 1520, 1483, 1384, 1325, 905, 726. HRMS (ESI-MS) m/z calcd for $C_{27}H_{22}N_3OS$ $[M + H]^+$ 436.1484 found 436.1497.

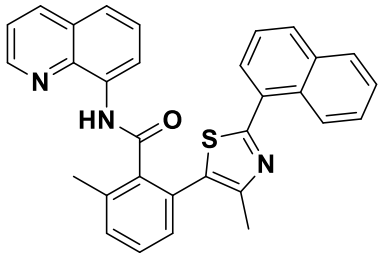


2-[2-(4-chlorophenyl)-4-methyl-1,3-thiazol-5-yl]-6-methyl-*N*-(quinolin-8-yl)benzamide (3b): The title compound was synthesized following General Procedure A. Light yellow solid in 89 % (83.7 mg, 0.17 mmol), mp = 80 – 82 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.82 (s, 1H), 8.77 (dd, *J* = 6.9, 2.1 Hz, 1H), 8.68 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.10 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.69 – 7.63 (m, 2H), 7.53 – 7.45 (m, 2H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.41 – 7.35 (m, 2H), 7.33 – 7.24 (m, 3H), 2.54 (s, 3H), 2.44 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.22, 165.04, 151.11, 148.13, 138.82, 138.35, 136.54, 136.39, 135.81, 134.18, 131.91, 131.21, 129.59, 129.39, 129.29, 129.07, 129.00, 128.04, 127.63, 127.47, 122.16, 121.71, 116.94, 19.95, 15.99. FTIR (ATR, cm^{-1}): 3343, 3188, 2943, 1674, 1523, 1483, 1424, 1326, 826, 789. HRMS (ESI-MS) m/z calcd for $C_{27}H_{21}ClN_3OS$ $[M + H]^+$ 470.1094 found 470.0925.

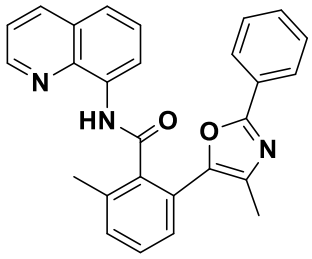


2-[2-(4-methoxyphenyl)-4-methyl-1,3-thiazol-5-yl]-6-methyl-*N*-(quinolin-8-yl)benzamide (3c): The title compound was synthesized following General Procedure A. Light yellow solid in 72 % (67.0 mg, 0.14 mmol), mp = 85 – 87 °C. ^{1}H NMR (400 MHz,

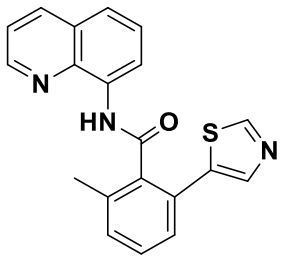
$CDCl_3$): δ 9.82 (s, 1H), 8.79 (dt, *J* = 7.4, 1.3 Hz, 1H), 8.66 (ddd, *J* = 4.1, 1.7, 0.7 Hz, 1H), 8.09 – 7.99 (m, 1H), 7.71 – 7.61 (m, 2H), 7.53 – 7.38 (m, 3H), 7.38 – 7.28 (m, 3H), 6.86 – 6.75 (m, 2H), 3.77 (s, 3H), 2.54 (s, 3H), 2.44 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.28, 166.22, 160.93, 150.64, 148.12, 138.78, 138.41, 136.27, 136.25, 134.28, 130.88, 129.44, 129.35, 129.25, 128.09, 127.94, 127.79, 127.33, 126.54, 121.98, 121.61, 116.68, 114.10, 55.38, 19.92, 16.06. FTIR (ATR, cm^{-1}): 3333, 3062, 2926, 1671, 1518, 1482, 1460, 1423, 1325, 1252, 1171, 905, 726. HRMS (ESI-MS) m/z calcd for $C_{28}H_{24}N_3O_2S$ $[M + H]^+$ 466.1589 found 466.1578.



2-methyl-6-[4-methyl-2-(naphthalene-1-yl)-1,3-thiazol-5-yl]-*N*-(quinolin-8-yl)benzamide (3d): The title compound was synthesized following General Procedure A. Light yellow solid in 93 % (90.3 mg, 0.18 mmol), mp = 208 – 210 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 8.87 (dd, *J* = 7.5, 1.5 Hz, 1H), 8.68 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.07 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 2H), 7.79 (ddt, *J* = 9.2, 8.1, 1.0 Hz, 2H), 7.57 – 7.30 (m, 9H), 7.21 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 2.60 (s, 3H), 2.59 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.27, 165.41, 150.73, 148.17, 138.70, 138.34, 136.69, 136.32, 134.34, 133.80, 131.09, 130.79, 130.65, 130.19, 130.05, 129.43, 129.30, 129.15, 128.18, 128.15, 127.96, 127.44, 127.03, 126.12, 125.51, 124.89, 122.01, 121.72, 116.59, 20.03, 16.19. FTIR (ATR, cm^{-1}): 3339, 3057, 2919, 1672, 1519, 1482, 1423, 1325, 1263, 906, 729. HRMS (ESI-MS) m/z calcd for $C_{31}H_{24}N_3OS$ $[M + H]^+$ 486.1640 found 486.1650.

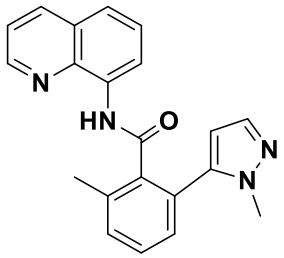


2-methyl-6-(4-methyl-2-phenyl-1,3-oxazol-5-yl)-*N*-(quinolin-8-yl)benzamide (3e): The title compound was synthesized following General Procedure A. White solid in 74 % (62.0 mg, 0.14 mmol), mp = 148 – 150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.92 (s, 1H), 8.87 (dd, *J* = 7.2, 1.8 Hz, 1H), 8.62 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.08 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.65 – 7.58 (m, 2H), 7.52 – 7.39 (m, 4H), 7.38 – 7.30 (m, 2H), 7.21 – 7.15 (m, 1H), 7.05 – 6.98 (m, 2H), 2.56 (s, 3H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.98, 160.09, 148.33, 144.30, 138.54, 136.77, 136.33, 136.23, 135.24, 134.47, 130.84, 129.90, 129.43, 128.33, 128.01, 127.39, 126.99, 126.30, 126.28, 126.12, 122.01, 121.71, 117.06, 19.86, 13.10. FTIR (ATR, cm^{-1}): 3346, 3079, 2924, 1677, 1519, 1482, 1424, 1325, 1264, 1028, 898, 711. HRMS (ESI-MS) m/z calcd for $C_{27}H_{22}N_3O_2$ $[M + H]^+$ 420.1712 found 420.1728.

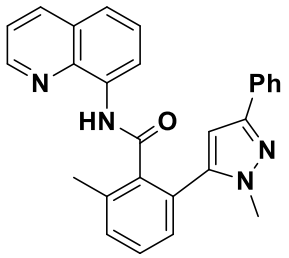


2-methyl-*N*-(quinolin-8-yl)-6-(1,3-thiazol-5-yl)benzamide (3f): The title compound was synthesized following General Procedure B. Bright yellow solid in 90 % (62.1 mg, 0.18 mmol), mp = 56 – 58 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H), 8.86 (dd, *J* = 7.1, 1.9 Hz, 1H), 8.67 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.62 (d, *J* = 0.6 Hz, 1H), 8.13 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.02 (t, *J* = 0.5 Hz, 1H), 7.59 – 7.49 (m, 2H), 7.44 – 7.37 (m, 3H), 7.36 – 7.31 (m, 1H), 2.52 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.64, 153.37, 148.35, 141.91, 138.50, 137.32, 136.46, 136.33, 136.17, 134.16, 130.90, 129.56, 128.40, 128.25, 128.05, 127.46, 122.34, 121.77, 117.13, 19.75. FTIR (ATR, cm^{-1}): 3339, 3003,

2916, 1672, 1519, 1483, 1424, 1386, 1325, 874, 789, 754. HRMS (ESI-MS) m/z calcd for $C_{20}H_{16}N_3OS$ $[M + H]^+$ 346.1014 found 346.1028.

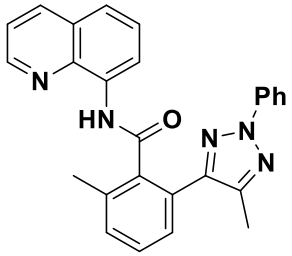


2-methyl-6-(1-methyl-1H-pyrazol-5-yl)-*N*-(quinolin-8-yl)benzamide (3g): The title compound was synthesized following General Procedure B. Light yellow solid in 74 % (50.6 mg, 0.14 mmol), mp = 140 – 142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.69 (s, 1H), 8.74 (dd, *J* = 6.3, 2.7 Hz, 1H), 8.69 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.13 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.47 – 7.36 (m, 3H), 7.28 – 7.20 (m, 2H), 6.33 (d, *J* = 1.9 Hz, 1H), 3.84 (s, 3H), 2.54 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.13, 148.15, 140.83, 138.45, 138.33, 136.42, 136.21, 134.10, 131.26, 129.22, 128.44, 127.99, 127.97, 127.37, 122.07, 121.72, 116.66, 107.38, 37.24, 19.77. FTIR (ATR, cm^{-1}): 3326, 3067, 2922, 1675, 1523, 1483, 1424, 1326, 826, 753. HRMS (ESI-MS) m/z calcd for $C_{21}H_{19}N_4O$ $[M + H]^+$ 343.1559 found 343.1570.

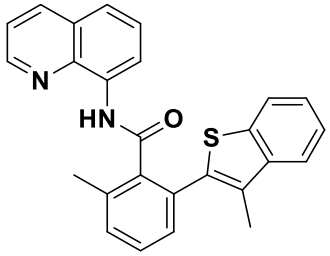


2-methyl-6-(1-methyl-3-phenyl-1H-pyrazol-5-yl)-*N*-(quinolin-8-yl)benzamide (3h): The title compound was synthesized following General Procedure B. Light yellow solid in 70 % (58.5 mg, 0.14 mmol), mp = 92 – 93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 8.76 (dd, *J* = 7.2, 1.6 Hz, 1H), 8.67 (dd, *J* = 4.3, 1.6 Hz, 1H), 8.06 (dt, *J* = 8.3, 1.6 Hz, 1H), 7.55 – 7.37 (m, 6H), 7.34 (ddd, *J* = 8.2, 4.3, 1.4 Hz, 1H), 7.31 – 7.14 (m, 4H), 6.68 (d, *J* = 1.5 Hz, 1H), 3.86 (s, 3H), 2.57 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ

167.15, 150.49, 148.17, 142.38, 138.42, 138.39, 136.42, 134.15, 133.46, 131.44, 129.32, 128.44, 128.43, 128.33, 128.10, 128.02, 127.41, 127.40, 125.53, 122.15, 121.64, 116.81, 104.92, 37.43, 19.88. FTIR (ATR, cm^{-1}): 3337, 3134, 2929, 1672, 1520, 1483, 1424, 1325, 906, 723. HRMS (ESI-MS) m/z calcd for $C_{27}H_{23}N_4O$ $[M + H]^+$ 419.1872 found 419.1889.

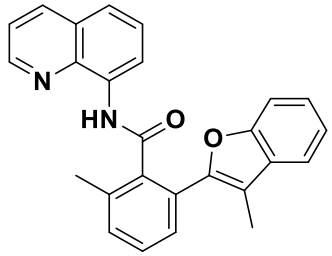


2-methyl-6-(5-methyl-2-phenyl-2H-1,2,3-triazol-4-yl)-*N*-(quinolin-8-yl)benzamide (3i): The title compound was synthesized following General Procedure A. Yellow solid in 40 % (33.5 mg, 0.08 mmol), mp = 140 – 142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.95 (s, 1H), 8.85 (dd, *J* = 7.3, 1.7 Hz, 1H), 8.60 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.09 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.67 – 7.60 (m, 2H), 7.54 – 7.41 (m, 4H), 7.41 – 7.36 (m, 1H), 7.33 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.15 – 7.08 (m, 3H), 2.60 (s, 3H), 2.44 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.98, 148.26, 145.67, 143.89, 139.56, 138.59, 137.65, 136.70, 136.22, 134.59, 131.05, 129.31, 128.85, 128.16, 128.00, 127.41, 126.70, 121.84, 121.58, 118.26, 116.86, 19.98, 11.21. FTIR (ATR, cm^{-1}): 3344, 3059, 2923 1673, 1595, 1519, 1482, 1325, 907, 729. HRMS (ESI-MS) m/z calcd for $C_{26}H_{22}N_5O$ $[M + H]^+$ 420.1824 found 420.1839.

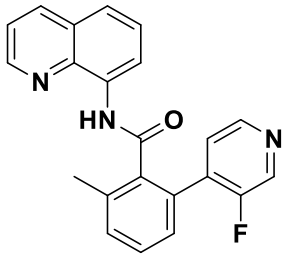


2-methyl-6-(3-methyl-1-benzothiophen-2-yl)-*N*-(quinolin-8-yl)benzamide (3j): The title compound was synthesized following General Procedure B. Light yellow solid in 70

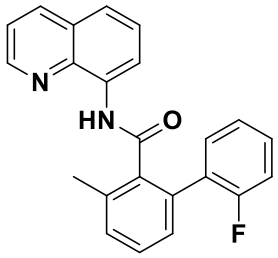
% (57.1 mg, 0.14 mmol), mp = 211 – 212 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (s, 1H), 8.75 (dd, *J* = 7.4, 1.6 Hz, 1H), 8.63 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.02 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.62 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.56 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.47 – 7.40 (m, 3H), 7.39 – 7.36 (m, 1H), 7.36 – 7.30 (m, 2H), 7.27 – 7.21 (m, 1H), 7.17 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1H), 2.56 (s, 3H), 2.38 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 167.42, 147.97, 140.35, 139.67, 138.72, 138.42, 136.23, 136.19, 135.60, 134.45, 132.05, 130.87, 130.03, 129.46, 129.06, 127.89, 127.34, 124.14, 123.88, 122.06, 122.05, 121.78, 121.51, 116.64, 20.03, 12.76. FTIR (ATR, cm^{-1}): 3340, 3061, 2919, 1671, 1520, 1482, 1325, 905, 727. HRMS (ESI-MS) m/z calcd for $C_{26}H_{21}N_2OS$ $[M + H]^+$ 409.1375 found 409.1383.



2-methyl-6-(3-methyl-1-benzofuran-2-yl)-*N*-(quinolin-8-yl)benzamide (3k): The title compound was synthesized following General Procedure B. Light yellow solid in 36 % (28.2 mg, 0.07 mmol), mp = 135 – 137 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 8.83 (dd, *J* = 7.6, 1.0 Hz, 1H), 8.60 (dd, *J* = 4.3, 1.7, 0.7 Hz, 1H), 8.09 – 8.01 (m, 1H), 7.55 – 7.41 (m, 4H), 7.41 – 7.28 (m, 3H), 7.08 – 6.97 (m, 3H), 2.60 (s, 3H), 2.36 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 167.90, 154.28, 149.95, 148.03, 138.50, 137.35, 136.68, 136.15, 134.72, 131.14, 130.38, 129.21, 128.68, 127.91, 127.70, 127.36, 124.17, 122.11, 121.73, 121.49, 119.28, 116.65, 113.51, 110.86, 20.00, 9.16. FTIR (ATR, cm^{-1}): 3342, 3052, 2986, 1673, 1519, 1482, 1384, 1325, 1079, 1263, 905, 728. HRMS (ESI-MS) m/z calcd for $C_{26}H_{21}N_2O_2$ $[M + H]^+$ 393.1603 found 393.1618.

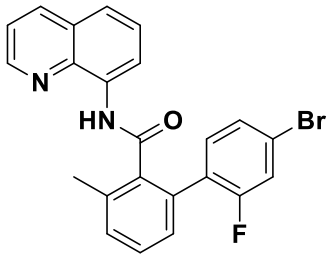


2-(3-fluoropyridin-4-yl)-6-methyl-*N*-(quinolin-8-yl)benzamide (3l): The title compound was synthesized following General Procedure B. Yellow solid in 35 % (25.0 mg, 0.07 mmol), mp = 154 – 155 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 8.72 – 8.65 (m, 2H), 8.34 (d, *J* = 1.7 Hz, 1H), 8.25 (dd, *J* = 4.9, 0.9 Hz, 1H), 8.11 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.51 – 7.48 (m, 2H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.43 – 7.37 (m, 3H), 7.32 – 7.28 (m, 1H), 2.57 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.95, 148.30, 145.49, 145.44, 138.61, 138.46, 138.36, 137.35, 136.52, 136.40, 135.74, 135.61, 134.04, 131.54, 130.79, 129.44, 127.98, 127.91, 127.89, 127.35, 125.53, 122.26, 121.80, 116.75, 20.03. ^{19}F NMR (376 MHz, $CDCl_3$) δ -130.14 (d, *J* = 6.5 Hz). FTIR (ATR, cm^{-1}): 3333, 3132, 1675, 1523, 1484, 1424, 1326, 827, 722. HRMS (ESI-MS) m/z calcd for $C_{22}H_{17}FN_3O$ $[M + H]^+$ 358.1356 found 358.1370.

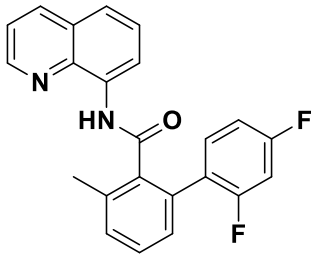


2'-fluoro-3-methyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (3r): The title compound was synthesized following General Procedure A. White solid in 70 % (49.8 mg, 0.14 mmol), mp = 78 – 80 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.77 (s, 1H), 8.72 (dd, *J* = 6.8, 2.2 Hz, 1H), 8.67 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.09 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.53 – 7.36 (m, 5H), 7.34 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.30 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.12 – 7.04 (m, 1H), 6.99 (td, *J* = 7.5, 1.3 Hz, 1H), 6.93 (ddd, *J* = 9.7, 8.1, 1.3 Hz, 1H), 2.55 (s, 3H).

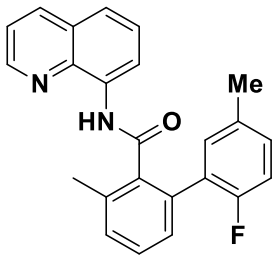
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 167.73, 159.75 (d), 148.17, 138.52, 137.77, 136.19, 136.01, 134.45, 133.54, 131.60 (d), 130.35, 129.48 (d), 129.08, 128.47, 128.46, 127.89, 127.73, 127.36, 123.91 (d), 121.71 (d), 116.54, 115.60 (d), 20.04. ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.43 (td, *J* = 8.7, 5.3 Hz). FTIR (ATR, cm^{-1}): 3337, 2925, 1673, 1519, 1482, 1423, 1325, 1233, 1026, 826, 753. HRMS (ESI-MS) m/z calcd for $C_{23}H_{18}FN_2O$ $[M + H]^+$ 357.1403 found 357.1407.



4'-bromo-2'-fluoro-3-methyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (3s): The title compound was synthesized following General Procedure A. White solid in 58 % (50.4 mg, 0.11 mmol), mp = 67 – 68 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 8.73 (dd, *J* = 6.0, 3.0 Hz, 1H), 8.68 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.12 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.54 – 7.48 (m, 2H), 7.45 – 7.38 (m, 2H), 7.35 (ddd, *J* = 7.6, 1.4, 0.7 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.27 – 7.23 (m, 1H), 7.19 – 7.10 (m, 2H), 2.55 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 167.47, 159.54 (d), 148.24, 138.51, 137.63, 136.34, 136.12, 134.26, 132.61 (d), 132.44, 130.70, 129.20, 128.33, 127.98, 127.38, 127.31 (d), 127.01 (d), 122.06, 121.91 (d), 121.73, 119.32 (d), 116.75, 20.04. ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.36 (t, *J* = 8.6 Hz). FTIR (ATR, cm^{-1}): 3343, 3064, 1675, 1523, 1483, 1424, 1386, 1326, 892, 790. HRMS (ESI-MS) m/z calcd for $C_{23}H_{17}BrFN_2O$ $[M + H]^+$ 435.0508 found 435.0505.

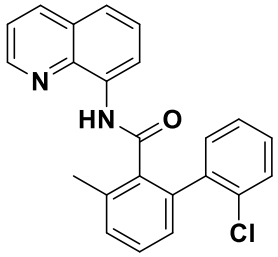


2',4'-difluoro-3-methyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (3t): The title compound was synthesized following General Procedure A. White solid in 55 % (41.1 mg, 0.10 mmol). mp = 136 – 138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.77 (s, 1H), 8.72 (dd, *J* = 6.1, 2.9 Hz, 1H), 8.68 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.12 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.45 – 7.37 (m, 3H), 7.37 – 7.32 (m, 1H), 7.29 – 7.22 (m, 1H), 6.79 – 6.65 (m, 2H), 2.54 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.61, 162.24 (dd), 159.42 (dd), 148.20, 138.48, 137.89, 136.36, 136.07, 134.29, 132.61, 132.33 (dd), 130.53, 129.16, 128.50, 127.97, 127.40, 123.97 (dd), 121.99, 121.72, 116.67, 111.18(dd), 104.01 (dd), 20.01. ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.75 – -110.93 (m). FTIR (ATR, cm^{-1}): 3342, 3059, 1673, 1519, 1482, 1423, 1385, 1326, 1266, 966, 791. HRMS (ESI-MS) m/z calcd for $C_{23}H_{17}F_2N_2O$ $[M + H]^+$ 375.1309 found 375.1318.

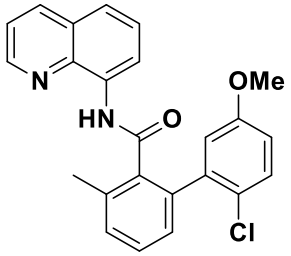


2'-fluoro-3,5'-dimethyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (3u): The title compound was synthesized following General Procedure A. White solid in 60 % (44.4 mg, 0.12 mmol), mp = 132 – 134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 8.74 (dd, *J* = 7.0, 1.9 Hz, 1H), 8.68 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.09 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.44 – 7.36 (m, 2H), 7.32 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.30 – 7.25 (m, 1H), 7.23 (dd, *J* = 7.3, 2.2 Hz, 1H), 6.86 – 6.74 (m, 2H), 2.55 (s, 3H), 2.14 (s, 3H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.81, 157.91 (d), 148.11, 138.51, 137.72,

136.22, 135.96, 134.52, 133.80, 133.22 (d), 131.95 (d), 130.25, 129.87, 129.79, 129.08, 128.41, 127.90, 127.37, 127.35 (d), 121.66 (d), 116.49, 115.18 (d), 20.57, 20.05. ^{19}F NMR (376 MHz, $CDCl_3$) δ -120.81 (q, *J* = 7.3 Hz). FTIR (ATR, cm^{-1}): 3344, 3061, 1677, 1522, 1483, 1424, 1385, 1326, 826, 760. HRMS (ESI-MS) m/z calcd for $C_{24}H_{20}FN_2O$ $[M + H]^+$ 371.1560 found 371.1572.

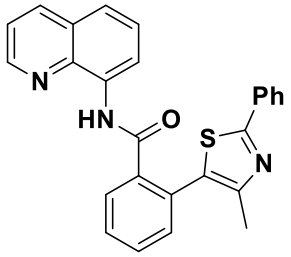


2'-chloro-3-methyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (3v): The title compound was synthesized following General Procedure A. White solid in 42 % (31.3 mg, 0.08 mmol), mp = 181 – 183 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 8.70 (dd, *J* = 4.1, 1.9 Hz, 1H), 8.68 – 8.62 (m, 1H), 8.08 (dq, *J* = 8.4, 1.4 Hz, 1H), 7.43 (td, *J* = 5.1, 1.5 Hz, 2H), 7.41 – 7.35 (m, 3H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.26 – 7.20 (m, 2H), 7.13 – 7.06 (m, 1H), 7.05 – 6.98 (m, 1H), 2.52 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.55, 148.07, 138.89, 138.46, 137.49, 137.03, 136.16, 135.83, 134.43, 133.27, 131.43, 130.21, 129.46, 128.96, 128.81, 128.17, 127.86, 127.32, 126.44, 121.75, 121.66, 116.46, 19.95. FTIR (ATR, cm^{-1}): 3339, 3127, 2915, 1676, 1522, 1483, 1425, 1326, 900, 730. HRMS (ESI-MS) m/z calcd for $C_{23}H_{18}ClN_2O$ $[M + H]^+$ 373.1108 found 373.1113.

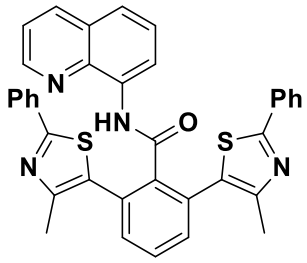


2'-chloro-5'-methoxy-3-methyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (3w): The title compound was synthesized following General Procedure A. Yellow solid

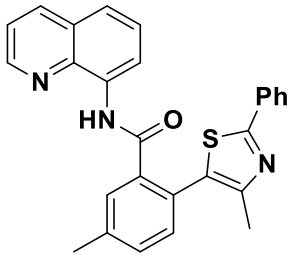
in 40 % (32.2 mg, 0.08 mmol), mp = 52 – 53 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (s, 1H), 8.73 – 8.68 (m, 2H), 8.08 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.49 – 7.43 (m, 2H), 7.42 – 7.36 (m, 2H), 7.34 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1H), 7.27 – 7.22 (m, 1H), 7.11 (d, *J* = 8.8 Hz, 1H), 6.96 (d, *J* = 3.0 Hz, 1H), 6.57 (dd, *J* = 8.8, 3.1 Hz, 1H), 3.64 (s, 3H), 2.55 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 167.55, 157.79, 148.03, 139.57, 138.43, 137.35, 137.08, 136.17, 135.90, 134.48, 130.27, 130.13, 128.85, 128.06, 127.86, 127.32, 124.58, 121.77, 121.64, 116.43, 115.94, 115.73, 55.61, 19.94. FTIR (ATR, cm^{-1}): 3333, 3063, 2958, 1671, 1519, 1482, 1423, 1324, 1228, 905, 728. HRMS (ESI-MS) m/z calcd for $C_{24}H_{20}ClN_2O_2$ $[M + H]^+$ 403.1213 found 403.1226.



2-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-*N*-(quinolin-8-yl)benzamide (3z): The title compound was synthesized following General Procedure A. Yellow solid in 45 % (37.9 mg, 0.09 mmol), mp = 138 – 140 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.20 (s, 1H), 8.85 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.49 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.11 – 8.05 (m, 1H), 8.03 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.85 – 7.76 (m, 2H), 7.62 – 7.55 (m, 2H), 7.55 – 7.48 (m, 2H), 7.45 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.36 (ddd, *J* = 4.9, 2.9, 1.6 Hz, 3H), 7.27 – 7.21 (m, 1H), 2.41 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 166.87, 166.32, 151.47, 148.04, 138.58, 137.11, 136.14, 134.60, 133.66, 132.54, 130.88, 130.17, 129.98, 129.59, 129.24, 129.17, 128.94, 127.92, 127.38, 126.40, 121.90, 121.56, 116.52, 15.93. FTIR (ATR, cm^{-1}): 3315, 2927, 1665, 1524, 1484, 1423, 1325, 755, 688. HRMS (ESI-MS) m/z calcd for $C_{26}H_{20}N_3OS$ $[M + H]^+$ 422.1327 found 422.1342.

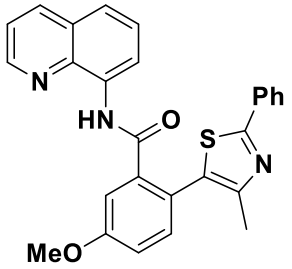


2,6-bis(4-methyl-2-phenyl-1,3-thiazol-5-yl)-*N*-(quinolin-8-yl)benzamide (3z'): The title compound was synthesized following General Procedure A. Yellow solid in 26 % (30.8 mg, 0.05 mmol), mp = 155 – 157 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (s, 1H), 8.64 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.56 (dd, *J* = 5.0, 4.0 Hz, 1H), 8.02 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.81 – 7.73 (m, 4H), 7.61 (dd, *J* = 8.9, 6.1 Hz, 1H), 7.58 – 7.53 (m, 2H), 7.41 – 7.37 (m, 2H), 7.37 – 7.28 (m, 7H), 2.48 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.70, 165.50, 151.35, 148.05, 139.88, 138.31, 136.30, 133.99, 133.52, 132.37, 130.70, 129.92, 129.45, 128.87, 128.48, 127.90, 127.36, 126.45, 122.07, 121.58, 116.86, 16.19. FTIR (ATR, cm^{-1}): 3329, 3056, 1672, 1521, 1484, 1424, 1384, 1326, 905, 726. HRMS (ESI-MS) m/z calcd for $C_{36}H_{27}N_4OS_2$ $[M + H]^+$ 595.1626 found 595.1646.

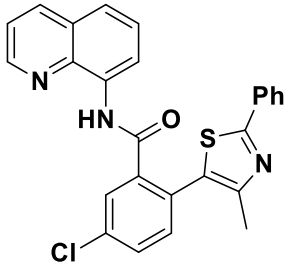


5-methyl-2-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-*N*-(quinolin-8-yl)benzamide (3aa): The title compound was synthesized following General Procedure A. Yellow solid in 86 % (74.9 mg, 0.17 mmol), mp = 147 – 148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.18 (s, 1H), 8.85 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.48 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.01 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.90 (q, *J* = 1.0 Hz, 1H), 7.85 – 7.76 (m, 2H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.44 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.40 – 7.31 (m, 5H), 7.23 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.49 (s, 3H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.65, 166.51, 151.34, 148.01, 139.35, 138.57, 136.83, 136.10, 134.63, 133.70, 132.45, 131.66, 130.73, 129.91, 129.33,

128.92, 127.90, 127.37, 126.49, 126.37, 121.84, 121.53, 116.50, 21.35, 15.89. FTIR (ATR, cm^{-1}): 3316, 3051, 2926, 1662, 1522, 1483, 1424, 1383, 1325, 906, 698. HRMS (ESI-MS) m/z calcd for $C_{27}H_{22}N_3OS$ $[M + H]^+$ 436.1484 found 436.1501.

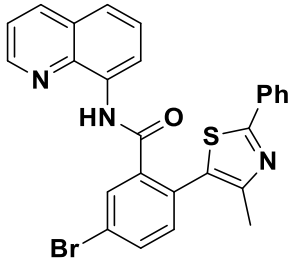


5-methoxy-2-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-*N*-(quinolin-8-yl)benzamide (3ab): The title compound was synthesized following General Procedure A. Light pink solid in 80 % (72.1 mg, 0.16 mmol), mp = 162 – 164 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.21 (s, 1H), 8.83 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.45 (dd, *J* = 4.2, 1.6 Hz, 1H), 7.98 (dt, *J* = 8.4, 1.8 Hz, 1H), 7.78 (dd, *J* = 6.7, 2.9 Hz, 2H), 7.61 (d, *J* = 2.7 Hz, 1H), 7.49 (t, *J* = 7.9 Hz, 1H), 7.45 – 7.36 (m, 2H), 7.36 – 7.30 (m, 3H), 7.20 (ddd, *J* = 8.1, 4.1, 1.9 Hz, 1H), 7.13 – 7.05 (m, 1H), 3.91 (s, 3H), 2.38 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.56, 166.02, 160.17, 151.48, 148.03, 148.02, 138.59, 138.14, 136.07, 134.56, 133.88, 133.77, 129.86, 129.14, 128.91, 127.89, 127.33, 126.33, 121.92, 121.54, 121.46, 117.57, 116.51, 114.57, 114.55, 55.77, 15.88. FTIR (ATR, cm^{-1}): 3317, 3052, 2960, 1661, 1523, 1483, 1424, 1385, 1326, 1038, 906, 727. HRMS (ESI-MS) m/z calcd for $C_{27}H_{22}N_3O_2S$ $[M + H]^+$ 452.1433 found 452.1449.

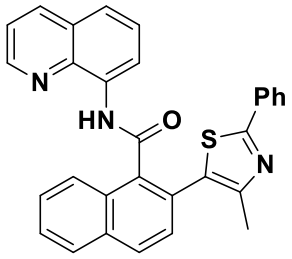


5-chloro-2-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-*N*-(quinolin-8-yl)benzamide (3ac): The title compound was synthesized following General Procedure A. Yellow solid in 61

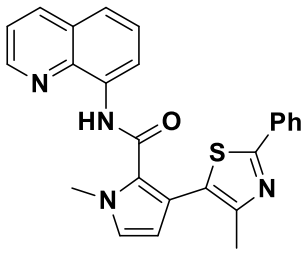
% (55.6 mg, 0.12 mmol), mp = 166 – 168 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.21 (s, 1H), 8.82 (dd, *J* = 7.5, 1.5 Hz, 1H), 8.48 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.09 (d, *J* = 2.3 Hz, 1H), 8.03 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.84 – 7.76 (m, 2H), 7.55 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.49 – 7.42 (m, 2H), 7.40 – 7.33 (m, 3H), 7.28 – 7.22 (m, 1H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.27, 164.77, 151.92, 148.13, 138.56, 138.39, 136.18, 135.47, 134.32, 133.84, 133.54, 130.99, 130.38, 130.14, 128.99, 128.00, 127.93, 127.92, 127.37, 126.43, 122.20, 121.64, 116.70, 15.95. FTIR (ATR, cm^{-1}): 3310, 3061, 2924, 1663, 1522, 1484, 1424, 1326, 908, 761, 728. HRMS (ESI-MS) m/z calcd for $C_{26}H_{19}ClN_3OS$ $[M + H]^+$ 456.0937 found 456.0955.



5-bromo-2-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-*N*-(quinolin-8-yl)benzamide (3ad): The title compound was synthesized following General Procedure A. Yellow solid in 55 % (55.0 mg, 0.11 mmol), mp = 156 – 158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.19 (s, 1H), 8.81 (dd, *J* = 7.5, 1.5 Hz, 1H), 8.47 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.24 (d, *J* = 2.1 Hz, 1H), 8.03 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.84 – 7.76 (m, 2H), 7.70 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.55 – 7.43 (m, 2H), 7.40 – 7.33 (m, 4H), 7.27 – 7.21 (m, 1H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.29, 164.65, 151.88, 148.12, 138.54, 136.16, 134.29, 133.98, 133.94, 133.52, 133.27, 130.14, 128.99, 128.47, 127.95, 127.35, 126.42, 123.45, 122.19, 121.63, 116.69, 15.95. FTIR (ATR, cm^{-1}): 3308, 3065, 1662, 1523, 1484, 1424, 1326, 905, 824, 726. HRMS (ESI-MS) m/z calcd for $C_{26}H_{19}BrN_3OS$ $[M + H]^+$ 500.0432 found 500.0452.



2-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-*N*-(quinolin-8-yl)naphthalene-1-carboxamide (3ae): The title compound was synthesized following General Procedure A. Light yellow solid in 80 % (75.4 mg, 0.16 mmol), mp = 98 – 100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.04 (s, 1H), 8.94 (dd, *J* = 7.6, 1.5 Hz, 1H), 8.61 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.29 – 8.21 (m, 1H), 8.07 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.04 – 7.99 (m, 1H), 7.98 – 7.93 (m, 1H), 7.80 – 7.72 (m, 2H), 7.63 – 7.51 (m, 4H), 7.48 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.36 – 7.28 (m, 4H), 2.51 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.78, 166.77, 151.42, 148.17, 138.44, 136.41, 136.29, 134.41, 133.54, 133.32, 130.49, 129.87, 129.85, 129.15, 128.83, 128.55, 128.26, 127.99, 127.89, 127.39, 127.27, 126.93, 126.41, 125.92, 122.21, 121.68, 116.85, 16.23. HRMS (ESI-MS) m/z calcd for $C_{30}H_{22}N_3OS$ $[M + H]^+$ 472.1484 found 472.1504.



1-methyl-3-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-*N*-(quinolin-8-yl)-1H-pyrrole-2-carboxamide (3af): The title compound was synthesized following General Procedure A. Yellow solid in 74 % (62.8 mg, 0.15 mmol), mp = 75 – 77 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.34 (s, 1H), 8.83 (dd, *J* = 7.7, 1.3 Hz, 1H), 8.30 (dd, *J* = 4.2, 1.7 Hz, 1H), 7.97 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.95 – 7.88 (m, 2H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.46 – 7.36 (m, 4H), 7.15 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.85 (d, *J* = 2.6 Hz, 1H), 6.27 – 6.22 (m, 1H), 4.12 (s, 3H), 2.37 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.73, 159.79, 152.40, 148.00, 138.61, 135.83, 135.15, 133.98, 129.86, 129.03, 127.91, 127.89, 127.25, 126.38,

124.94, 124.91, 121.50, 121.22, 117.17, 115.82, 111.50, 38.17, 15.92. FTIR (ATR, cm^{-1}): 3293, 2954, 1656, 1525, 1484, 1424, 1326, 824, 760. HRMS (ESI-MS) m/z calcd for $C_{25}H_{21}N_4OS$ $[M + H]^+$ 425.1436 found 425.1454.

Chapter 3: A Nickel-Catalyzed Sequential Oxidative Decarboxylative (Hetero)Arylation and Cyclization for the Synthesis of Phenanthridinones

3.1. Overview

As our work in Chapter 2 shows, we were able to achieve a new nickel-catalyzed oxidative decarboxylative (hetero)arylation of unactivated C –H bonds. During the optimization of the reaction conditions for the Ni-catalyzed ODC reaction, we noticed the formation of a small amount of byproduct, which we later characterized to be the phenanthridinone products. We found that phenanthridinones that contain heterocycles are limited under oxidative conditions as coupling partners. Knowing our new catalyst system works with heteroaromatic carboxylates, we should be able to achieve a sequential heteroarylation and cyclization to form heterocycle-containing phenanthridinones.

Phenanthridinones are key structures found in a variety of natural products and biologically active molecules[51] such as, anticancer therapeutics,[52] polymerase (PARP),[53] aurora kinase inhibitors,[54] antimalarial,[55] anti-HIV,[56] and antituberculosis activities[57] to name a few. In addition, phenanthridinone derivatives are also utilized in material sciences because of the planar heterocycle-containing system providing effective photoconducting and photovoltaic properties in optoelectronics and electroluminescence (Figure 1).[58]

Heterocycle-containing phenanthridinones, however, are less explored than their non-heterocycle-containing counterparts. The ability to synthesize a library of different heterocycle-containing phenanthridinones could prove valuable in a world of evolving diseases, since heterocycles are sometimes more potent than non-heterocycle drugs.[12]

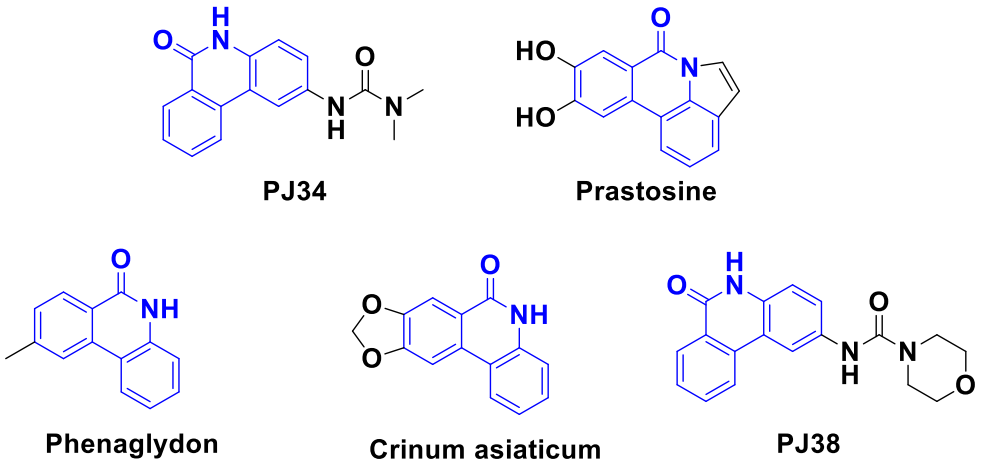
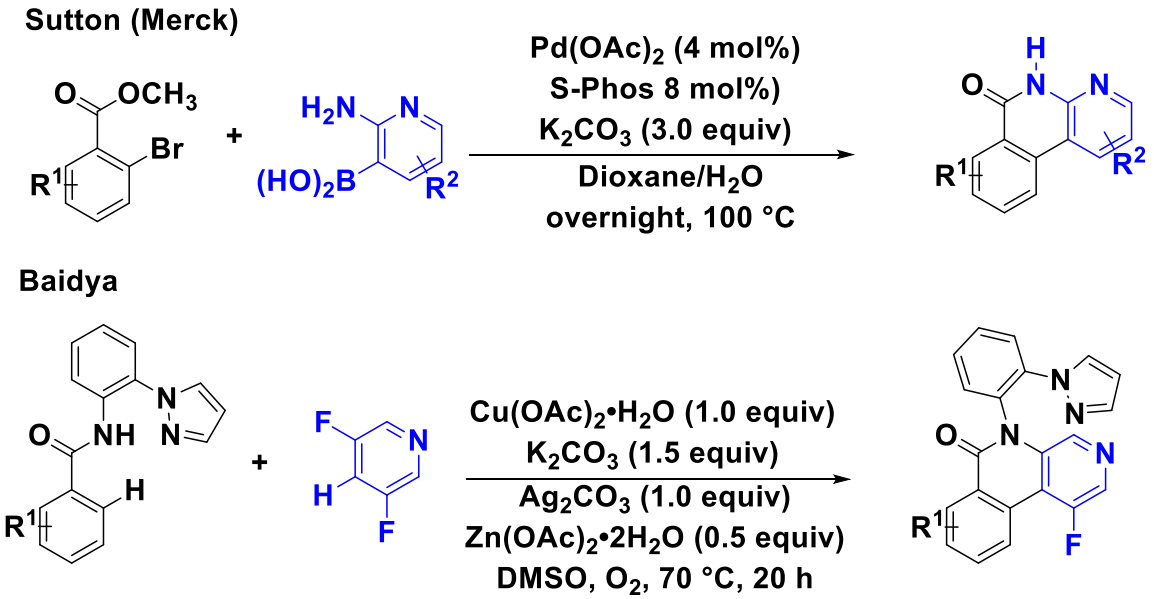


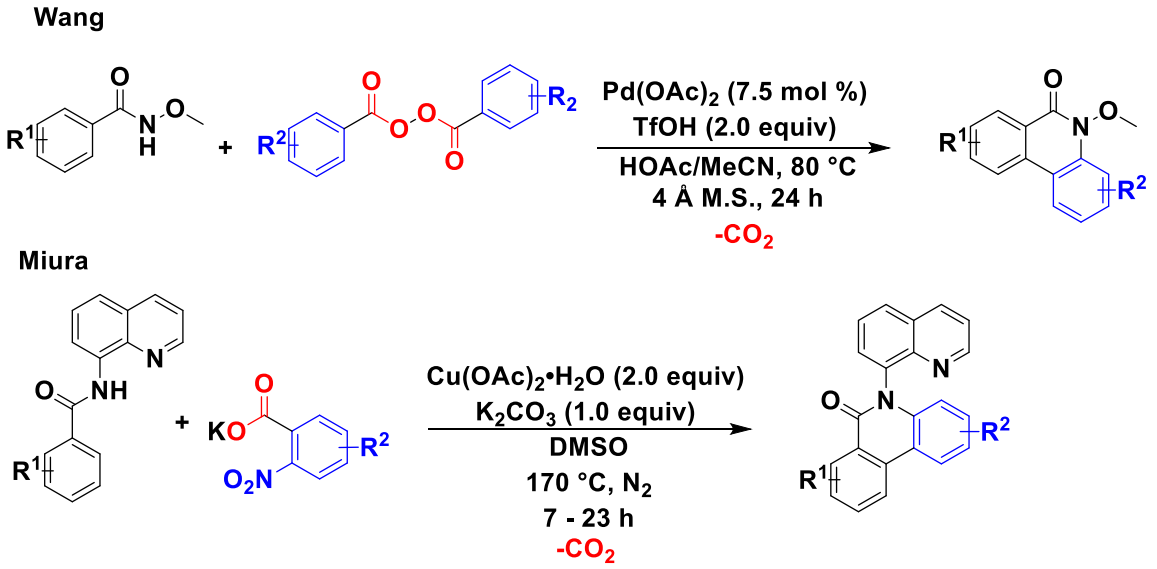
Figure 1. Phenanthridinones in medicine and natural products.

Phenanthridinones are typically synthesized from traditional cross-coupling reactions such as the Suzuki-Miyaura coupling or Buchwald-Hartwig amination reaction.[59] However, because of the inherent drawbacks associated with the required prefunctionalized starting materials, more recent efforts have led to oxidative variants with transition metals employing dehydrogenative coupling, yet these examples are limited to the use of simple arenes as coupling partners.[60] However, Baidya and co-workers recently reported a copper-mediated dehydrogenative annulation of benzamides with 3,5-difluorpyridine (Scheme 17).[61]



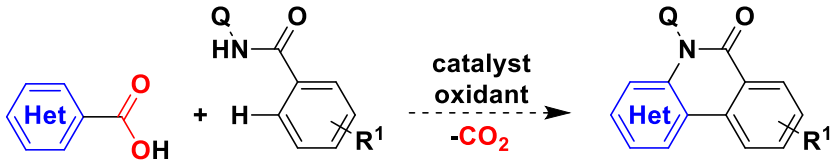
Scheme 17. Examples of heterocycle containing phenanthridinone syntheses.

Oxidative decarboxylative coupling reactions have been applied to the synthesis of phenanthridinones (Scheme 18). In 2014, Wang and co-workers reported the first synthesis of phenanthridinones utilizing a Pd-catalyzed ODC strategy with aryl acylperoxides and *N*-methoxybenzamides.[62] However, despite the fair reaction yields, the method was limited to aryl acylperoxides, which are commercially limited. Similarly, Miura and co-workers reported an analogous copper-mediated ODC reaction for the synthesis of phenanthridinones from *ortho*-nitrobenzoates.[65] While the work from Miura had advantages over Wang's (i.e. commercially available and shelf stable benzoates) both of their catalyst systems were limited to only 2-nitrobenzoates and aryl acylperoxides, heteroaryl carboxylates were ineffective coupling partners.



Scheme 18. Oxidative decarboxylative phenanthridinone syntheses.

At this time, there were no examples of a catalytic oxidative decarboxylative arylation and cyclization for the synthesis of heterocycle-containing phenanthridinones. From our studies in Chapter 2, we looked to extend our new methodology to couple heteroaromatic carboxylates with unactivated C–H bonds (Scheme 19).



Scheme 19. Targeted goal of achieving a sequential oxidative decarboxylative heteroarylation and cyclization with unactivated C–H bonds.

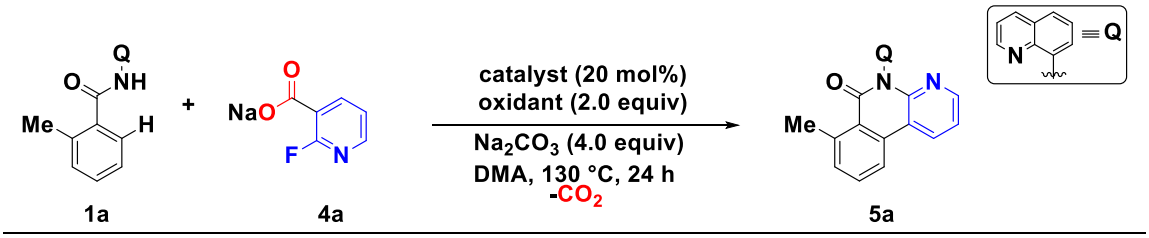
3.2. Results

3.2.1. Optimization of the Sequential Oxidative Decarboxylative (Hetero)arylation and Cyclization Reaction

We designed our reaction using 2-methyl-*N*-(quinolin-8-yl)benzamide and 2-fluoronicotinic carboxylate in the presence of nickel and silver. We begin by using $Ni(OAc)_2•4H_2O$ as our pre-catalyst in the presence of Ag_2CO_3 as our oxidant which generated the desired product **5a** in 25% yield (Table 3.1 entry 1). All other nickel salts tested provided low yields of the desired product in (<10%). $AgNO_3$ was the best oxidant

for this transformation when the loading was increased to 4.0 equivalents, while other oxidants explored (AgOPiv and AgOAc) gave lower yields (Table 3.1 entry 3 and 4). Finally, when we increased the loading of **5a** from 1.5 equivalents to 2.0 equivalents, the yield of the desired product increased to 81% (Table 3.1 entry 6). Therefore, the final optimized conditions employ 20 mol% of $Ni(OAc)_2•4H_2O$, $AgNO_3$ (4.0 equiv), and Na_2CO_3 (4.0 equiv) in DMA at 130 °C for 24 h.

Table 3.1. Optimization of the nickel-catalyzed sequential oxidative decarboxylative (hetero)arylation[a]



1a 4a 5a

entry	catalyst	oxidant	yield (%)[b]
1	$Ni(OAc)_2•4H_2O$	Ag_2CO_3	25
2	$Ni(acac)_2$	Ag_2CO_3	4
3[c]	$Ni(OAc)_2•4H_2O$	AgOPiv	63
4[c]	$Ni(OAc)_2•4H_2O$	AgOAc	51
5[a]	$Ni(OAc)_2•4H_2O$	Ag_3PO_4	35
6[c,e]	**$Ni(OAc)_2•4H_2O$**	**$AgNO_3$**	**81 (80)**[f]
7[c,e]	-	$AgNO_3$	0
8[e]	$Ni(OAc)_2•4H_2O$	-	0

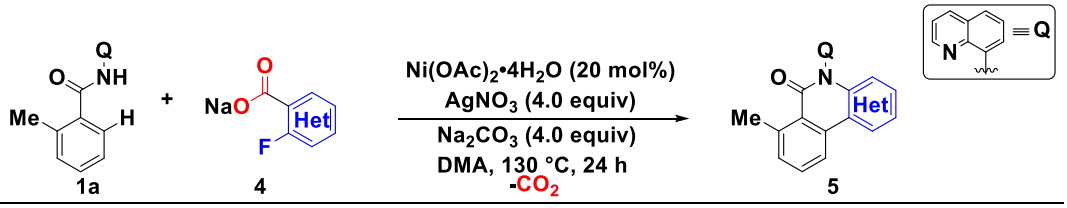
[a]Reaction conditions: **1a** (0.2 mmol), **4a** (0.3 mmol) in DMA (2 mL). [b]^{1}H NMR yield with 1,3,5-trimethoxybenzene as an internal standard. [c]Ag (4.0 equiv). [d]1.3 equiv Ag_3PO_4 (4.0 equiv of Ag) [e]**4a** (0.4 mmol). [f]Isolated yield.

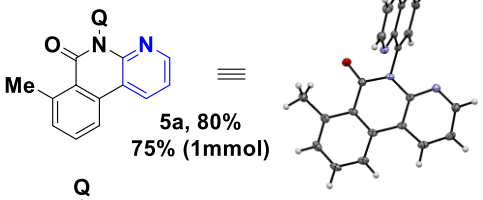
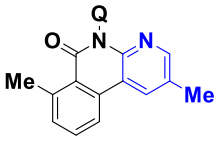
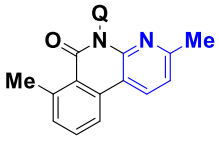
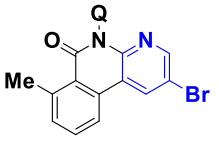
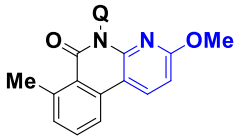
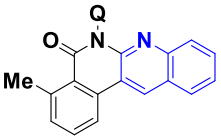
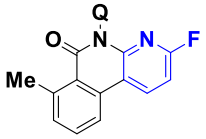
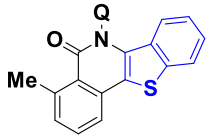
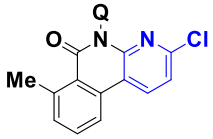
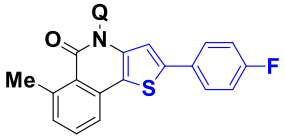
3.2.2. Scope of the Sequential Oxidative Decarboxylative (Hetero)arylation and Cyclization Reaction

With the optimized conditions in hand, we turned our attention to the heteroaromatic carboxylate scope (Table 3.2). The reaction is compatible with both electron-withdrawing (**5d**, **5e**, and **5g**), and electron-donating (**5b**, **5c**, and **5f**) substituents on the nicotinic carboxylate. We found that substituents in the C–6 position of the nicotinate resulted in lower yields (**4c** – **4e**) than their unsubstituted counterpart (**4a**). Analogous to the ODC reaction described in Chapter 2, this new catalyst system also tolerates bromo- and

chloro-substitution (**5e** and **5g**) allowing for further functionalization in subsequent cross-coupling reactions. This new catalyst method could also be conducted on a 1 mmol scale without a significant reduction in yield (75% of **5a**). To our delight, we found that other heteroaromatic carboxylates also couple under this new reaction system. Quinoline and thiophenes are found in pharmacologically active compounds[63] and material sciences[64] and the corresponding carboxylates (**5h-5j**) also proved to be competent coupling partners under these catalytic conditions.

Table 3.2. Ni-catalyzed oxidative decarboxylative arylation and cyclization heteroaromatic carboxylate scope[a]

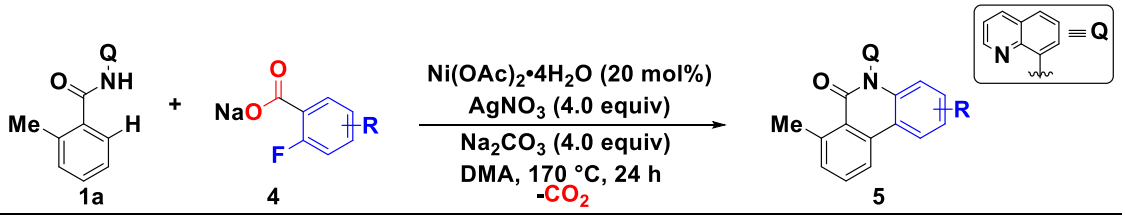


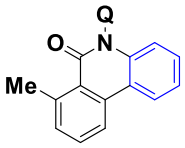
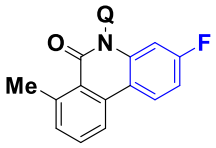
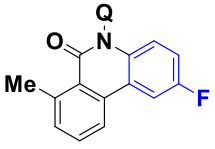
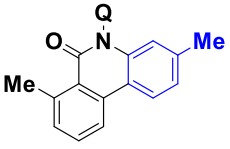
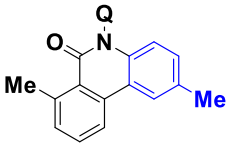
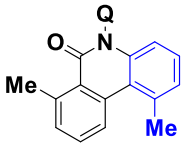
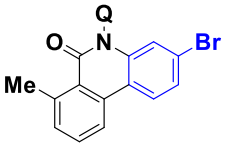
Entry			Entry		
1		5a, 80% 75% (1mmol)	6		5f, 70%
2		5b, 67%	7		5g, 40%
3		5c, 36%	8		5h, 51%
4		5d, 29%	9		5i, 44%[b]
5		5e, 27%	10		5j, 23%[c]

[a]Isolated yields. Reaction conditions: **1a** (0.2 mmol), **4** (0.4 mmol) in DMA (2 mL). [b]130 °C for 8 h then 170 °C for 16 h [c]170 °C.

This new catalyst system also worked with substituted benzoates as seen in our previous ODC reaction (Table 3.3). To our surprise, the sequential oxidative decarboxylative arylation proceeded smoothly at 170 °C. A variety of different electron-donating (**5l** and **5o)** and electron-withdrawing groups (**5k**, **5m**, and **5n**) were tolerated on the benzoates. However, we did notice di-*ortho*-substituted 2-fluoro-6-methylbenzaote (**4p**) was an ineffective coupling partner under these reaction conditions. This new method illustrates the ability to couple and cyclize not only heteroaromatic carboxylates but also *ortho*-fluorobenzoates.

Table 3.3. Ni-catalyzed oxidative decarboxylative arylation and cyclization benzoate scope[a]



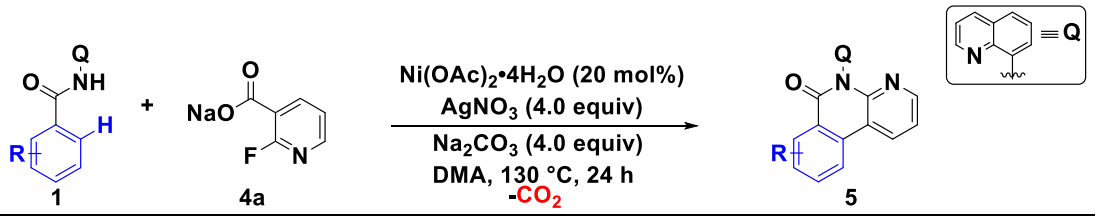
Entry			Entry		
1		5j, 68%	5		5n, 68%
2		5k, 62%	6		5o, 50%
3		5l, 56%	7		5p, 0%
4		5m, 36%			

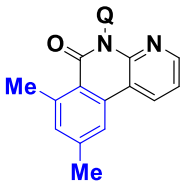
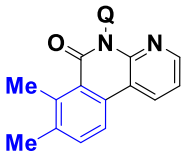
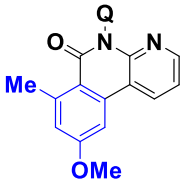
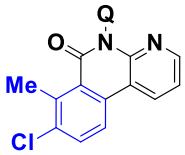
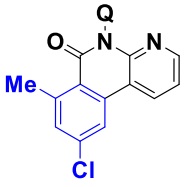
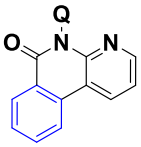
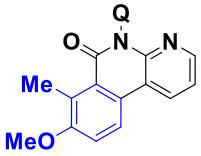
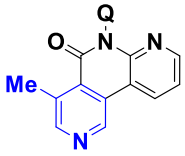
[a]Isolated yields. Reaction conditions: **1a** (0.2 mmol), **4** (0.4 mmol) in DMA (2 mL).

Finally, we explored the scope of the substituted benzamides with the 2-fluoronicotinic carboxylate (Table 3.4). Benzamide substrates with electron-donating groups *para* to the

benzamide moiety (**5q** and **5r**) gave higher yields than the electron-withdrawing group (**5s**). In addition, substrates bearing electron-donating groups in the *meta*-position (**5t** and **5u**) gave higher yields (54% and 70%) than those with electron-withdrawing groups (**5v**, 31%). We did notice that in the absence of an *ortho*-substituent on the benzamide, product formation was reduced (**5w**). This new catalyst method also tolerates heterocyclic benzamides (**5x**) opening the potential to build a vast library of substituted phenanthridinones.

Table 3.4. Ni-catalyzed oxidative decarboxylative arylation and cyclization benzamide scope[a]



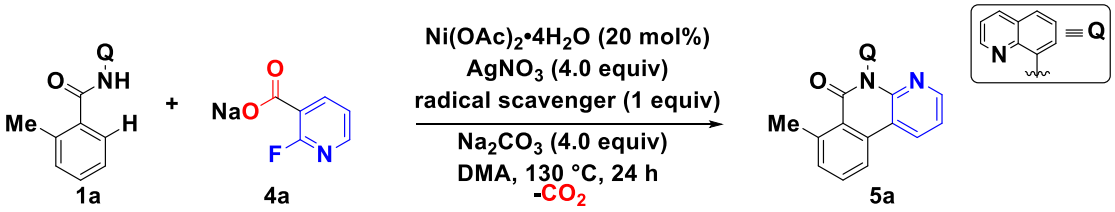
Entry			Entry		
1		5q, 75%	5		5u, 70%
2		5r, 71%	6		5v, 31%
3		5s, 63%	7		5w, 48%
4		5t, 54%	8		5x, 61%

[a]Isolated yields. Reaction conditions: **1** (0.2 mmol), **4a** (0.4 mmol) in DMA (2 mL).

3.2.3. Preliminary Mechanistic Studies of the Sequential Oxidative Decarboxylative (Hetero)Arylation and Cyclization Reaction

First, we conducted a series of radical trapping experiments under our reaction conditions to explore the possible formation of free radical intermediates. The reaction of **1a** and **4a** in the presence of 1.0 equiv of either TEMPO or DHA only slightly decreased the yield of the desired product **5a** (Table 3.5, entry 2 and 3). These data suggest there could be a well-defined silver-aryl intermediate in this reaction, analogous to the ODC reaction reported above (Chapter 2).

Table 3.5. Radical scavengers with the nickel-catalyzed sequential oxidative decarboxylative (hetero)arylation and cyclization reaction[a]

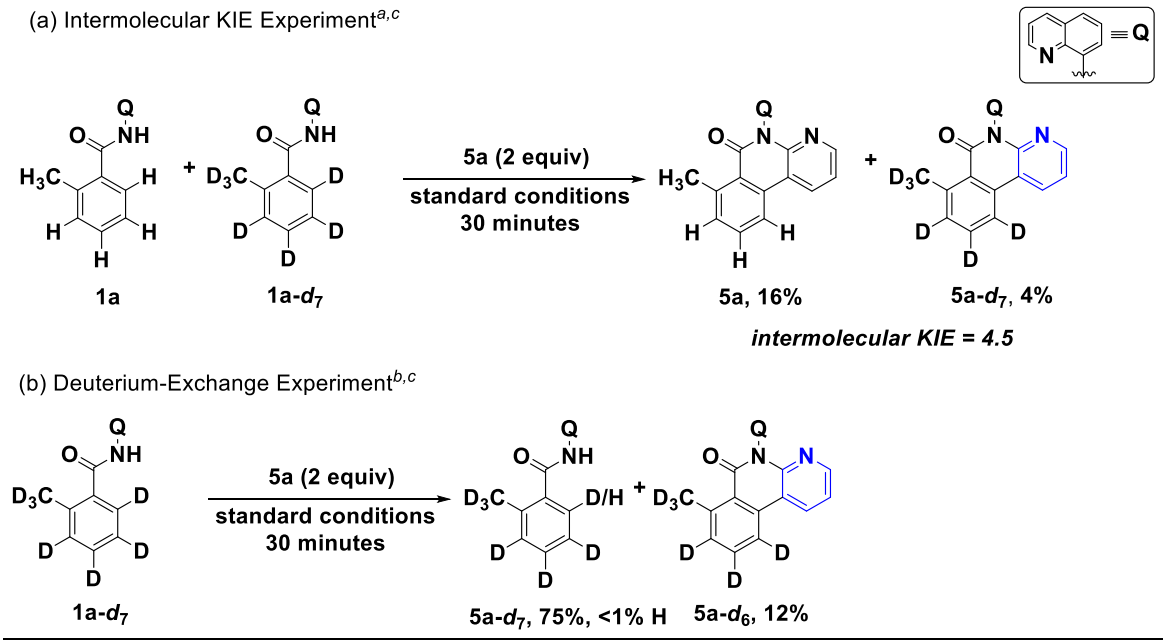


entry	Radical scav. (1 equiv)	yield (%)[b]
1	none	81
2	TEMPO	74
3	DHA	78

[a]Reaction conditions: Benzamide **1a** (0.2 mmol), heteroaromatic carboxylate **4a** (0.4 mmol), $Ni(OAc)_2$•$4H_2O$ (20 mol %), $AgNO_3$ (4.0 equiv), Na_2CO_3 (4.0 equiv), radical scavenger (1.0 equiv) in DMA (2 mL) for 24 h at 130 °C under a N_2 atmosphere. [b]^{1}H NMR yield with 1,3,5-trimethoxybenzene as an internal standard.

In order to gain insight into the C–H activation step, we carried out a deuterium/hydrogen exchange experiment. We measured the KIE from an intermolecular competition experiment with an equimolar mixture of **1a** and **1a-*d*$_7$** under our standard reaction conditions for 30 minutes. The KIE determined from the resulting mixture of **5a** and **5a-*d*$_7$** products is 4.5 (Scheme 20). Next, we carried out the deuterium/hydrogen exchange experiment of **1a-*d*$_7$** under the standard conditions for 30 min., the D content only dropped by >1%. These data indicate a primary isotope effect and that the C–H activation is irreversible.

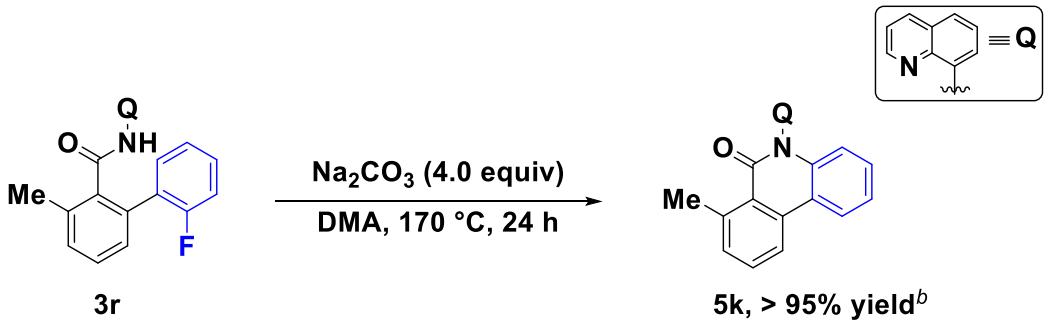
Scheme 20. Kinetic isotope effect of the nickel-catalyzed sequential oxidative decarboxylative.



[a]Reaction conditions: Benzamide **1a** (0.1 mmol), **1a-*d*$_7$** (0.1 mmol), heteroaromatic carboxylate **4a** (0.4 mmol), $Ni(OAc)_2$•$4H_2O$ (20 mol %), $AgNO_3$ (4.0 equiv), Na_2CO_3 (4.0 equiv) in DMA (2 mL) for 30 min. at 130 °C under a N_2 atmosphere. [b]Benzamide **1a-*d*$_7$** (0.2 mmol), heteroaromatic carboxylate **4a** (0.4 mmol), $Ni(OAc)_2$•$4H_2O$ (20 mol %), $AgNO_3$ (4.0 equiv), Na_2CO_3 (4.0 equiv) in DMA (2 mL) for 30 min. at 130 °C under a N_2 atmosphere. [c]^{1}H NMR yield with 1,3,5-trimethoxybenzene as an internal standard.

We found that Na_2CO_3 promotes a S_NAr-type cyclization following the oxidative decarboxylative coupling. From our ODC reaction reported above (Chapter 2), we prepared 2'-fluoro-3-methyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (**3r**) and heated the compound at 170 °C in the presence of Na_2CO_3 to mimic our benzoate reaction conditions to see if the compound would undergo cyclization. To our delight, compound **3r** underwent a S_NAr cyclization to generate the desired product (**5k**) in quantitative yield (Scheme 21). This type of cyclization has been seen before in other reactions.[65]

Scheme 21. Base promoted cyclization by S_NAr.[a]



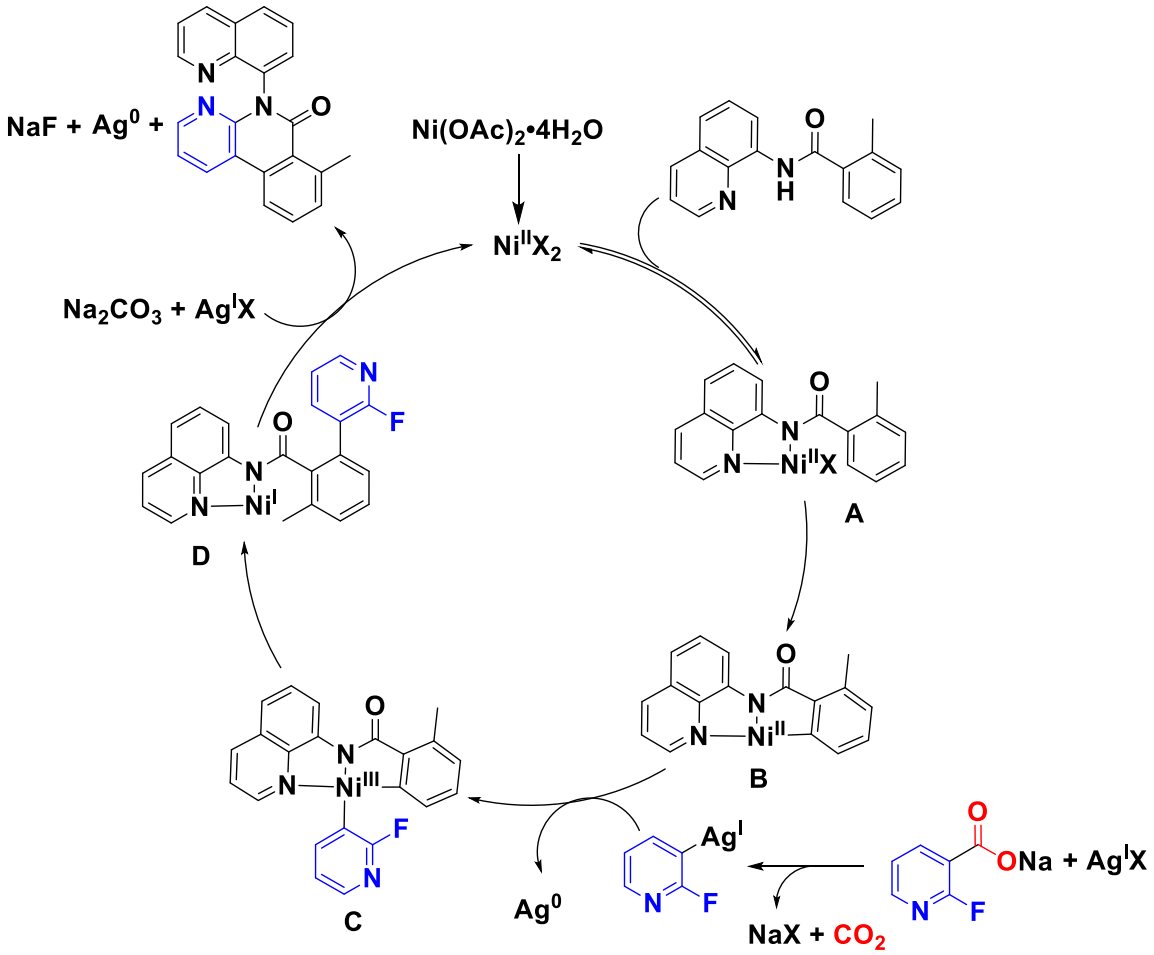
3r **5k, > 95% yield**[b]

[a]Reaction conditions: 2'-fluoro-3-methyl-N-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide **3r** (0.2 mmol) and Na_2CO_3 (4.0 equiv) in DMA (2 mL) for 24 h at 170 °C under a N_2 atmosphere. [b]^{1}H NMR yield with 1,3,5-trimethoxybenzene as an internal standard.

3.2.4. Proposed Reaction Mechanism of the Sequential Oxidative Decarboxylative (Hetero)Arylation and Cyclization Reaction

Based on the results above, we proposed a pathway for this new catalytic transformation that follows closely with that proposed for the Ni-catalyzed ODC reaction (Scheme 22). The catalyst undergoes ligand exchange with the amide and then C–H activation to form the nickel(II) metallacycle **B**. Transmetallation of the aryl fragment to the nickel(II) metallacycle with concomitant oxidation of nickel(II) to nickel(III) to form intermediate **C**. After reductive elimination of the high-valent nickel(III) intermediate to from the new C–C bond resulting in complex **D**. The desired product is then formed by S_NAr cyclization.

Scheme 22. Proposed reaction mechanism of the sequential oxidative decarboxylative (hetero)arylation and cyclization reaction.



3.3. Conclusion

In conclusion, we have developed a new method for the synthesis of heterocycle-containing phenanthridinones via an oxidative decarboxylative annulation reaction. This new method was not only effective for the coupling of heteroaromatic carboxylates but also *ortho*-fluoro benzoates. This new method could allow for the synthesis of a library of heterocycle-containing phenanthridinones with biological properties.

3.4. Experimental

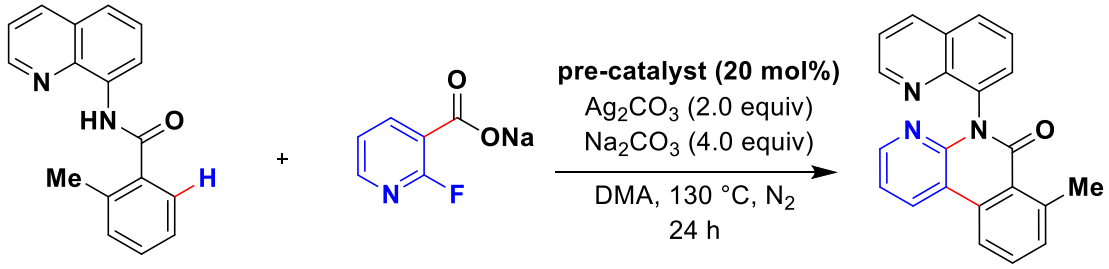
General Considerations. All manipulations were performed using standard Schlenk or glovebox techniques under a nitrogen atmosphere. All solvents (including dry DMA) were purchased from Alfa-Aesar, Fisher, or Cambridge Isotope Laboratories (deuterated solvents) and used as received. All other reagents were purchased from Maybridge, Oakwood, Acros, Alfa-Aesar, Astatech, Strem and CDN Isotopes and used without further purification. All NMR spectra were recorded at ambient temperature on an Agilent 400 MHz or JEOL 400 MHz (^{1}H, 400 MHz; ^{13}C{^{1}H}, 100 MHz; ^{19}F, 376 MHz) spectrometer. Chemical shifts are referenced to the residual solvent signals ($CDCl_3$: 7.26 ppm (^{1}H) and 77.2 ppm (^{13}C), DMSO-d_6: 2.50 ppm (^{1}H) and 39.5 ppm (^{13}C)).[45] High resolution mass spectra were obtained on a Thermofisher Scientific Q Exactive Mass Spectrometer. IR spectra were recorded on a PerkinElmer (Spectrum 100) FT-IR spectrometer. Column chromatography was performed using Silicycle Silica Flash P60 silica gel.

Optimization of the Oxidative Decarboxylative Annulation Reaction

Representative Procedure for the Optimization of the Oxidative Decarboxylative Annulation Reaction. An oven-dried 50 mL Schlenk tube with a stirring bar was charged with 2-fluoronicotinic acid **4a** (42.3 mg, 0.300 mmol), sodium carbonate (31.7 mg, 0.300 mmol), and dry DMA (1 mL). The reaction vessel was placed in a pre-heated oil bath and stirred for 0.5 h at 110 °C. The solvent was removed under reduced pressure until dry. 2-Methyl-*N*-(quinolin-8-yl) benzamide **1a** (52.4 mg, 0.200 mmol), $Ni(OAc)_2$•$4H_2O$ (9.9 mg, 0.040 mmol), Ag_2CO_3 (110 mg, 0.400 mmol), Na_2CO_3 (84 mg, 0.80 mmol) were added and the tube was evacuated and backfilled with nitrogen three times after which dry DMA (2 mL) was added *via* syringe. The reaction mixture was stirred at 130 °C for 24 h. Upon completion, the reaction tube was cooled to room temperature. The solution was diluted with dichloromethane (30 mL) and filtered through a pad of celite. The celite was then washed with dichloromethane (2 x 30 mL). The solvent was concentrated by rotary evaporation (to ~2 mL) and the remaining solvent was

removed under vacuum. A 1,3,5-trimethoxybenzene (5.00 mg) NMR standard was added to the residue and the crude mixture was dissolved in $CDCl_3$ for ^1H NMR analysis.

Optimization of the Precatalyst[a]

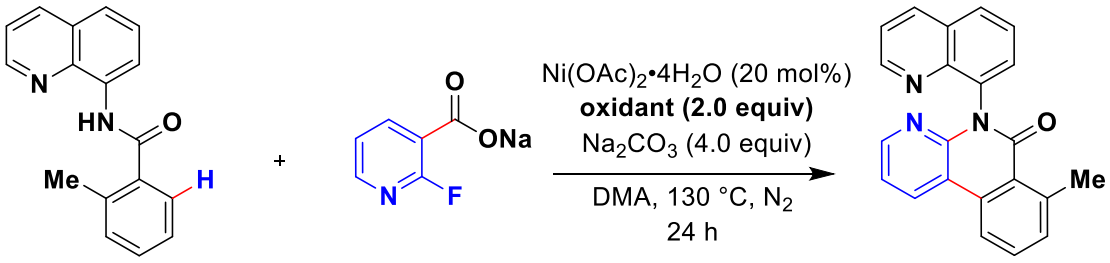


1a **4a** **5a**

entry	pre-catalyst	yield **5a** (%)[b]
1	$NiBr_2•H_2O$	3
2	$Ni(HCO_2)_2•2H_2O$	6
3	$Ni(acac)_2$	4
4	NiI_2	9
5	$NiCO_3•2Ni(OH)_2•H_2O$	1
6	$Ni(OTf)_2$	3
7	NiF_2	1
8	$NiCl_2$	5
9	$Ni(OAc)_2•4H_2O$	63
10[c]	$Ni(OAc)_2•4H_2O$	6
11[d]	$Ni(OAc)_2•4H_2O$	57
12	none	0

[a]Reaction conditions: **1a** (0.200 mmol), **4a** (0.300 mmol) in DMA (2 mL). [b]^1H NMR yield determined from integration using 1,3,5-trimethoxybenzene as an internal standard. [c]10 mol% [d]30 mol%

Optimization of the Oxidant[a]

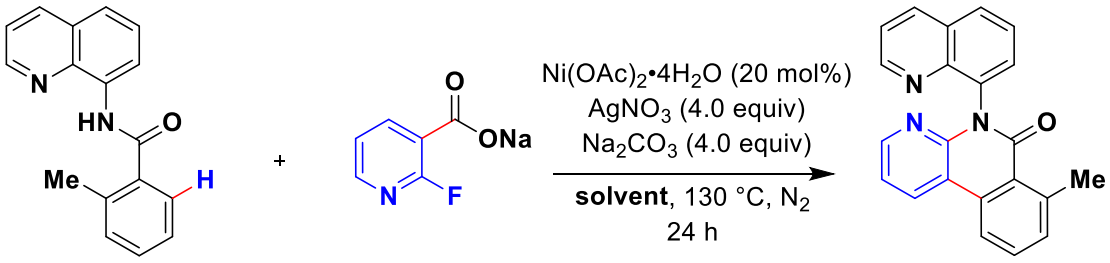


1a **4a** **5a**

entry	oxidant	yield **5a** (%)[b]
1	Ag_2CO_3	63
2[c]	$AgNO_3$	72
3[c]	AgOAc	51
4[c]	AgOPiv	63
5[f]	Ag_3PO_4	35
6	Ag_2O	18
7	oxone	0
8	O_2 (1 atm)	0
9[d]	$AgNO_3$	56
10[e]	$AgNO_3$	62
11	none	0

[a]Reaction conditions: **1a** (0.200 mmol), **4a** (0.300 mmol) in DMA (2 mL). [b]^{1}H NMR yield determined from integration using 1,3,5-trimethoxybenzene as an internal standard. [c] Ag (4.0 equiv) [d]3.0 equiv [e]5.0 equiv [f d]1.3 equiv Ag_3PO_4 (4.0 equiv of Ag)

Optimization of the Solvent[a]

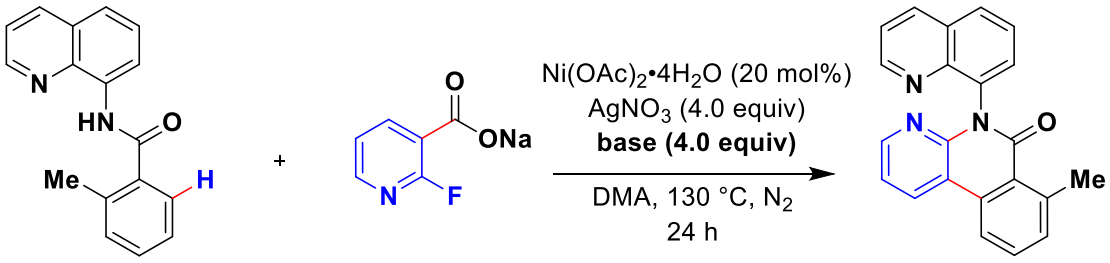


1a **4a** **5a**

entry	solvent	yield **5a** (%)[b]
1	DMA	72
2	DMF	52
3	NMP	63
4	DMSO	10
5	$PhCH_3$	0
6	MeCN	0
7[c]	DMA	38
8[d]	DMA	73

[a]Reaction conditions: **1a** (0.200 mmol), **4a** (0.300 mmol) in solvent (2 mL). [b]^{1}H NMR yield determined from integration using 1,3,5-trimethoxybenzene as an internal standard. [c]1 mL [d]3 mL

Optimization of the Base[a]

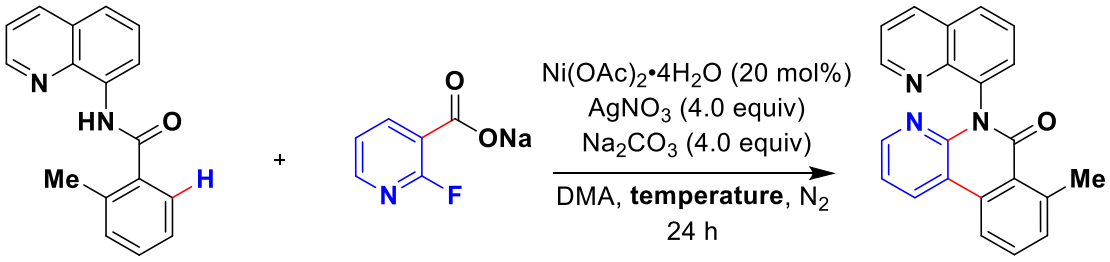


1a **4a** **5a**

entry	base	yield **5a** (%)[b]
1	Li_2CO_3	53
2	Na_2CO_3	72
3	K_2CO_3	18
4	NaOAc	40
5	pyridine	47
6	none	29

[a]Reaction conditions: **1a** (0.200 mmol), **4a** (0.300 mmol) in DMA (2 mL). [b]^{1}H NMR yield determined from integration using 1,3,5-trimethoxybenzene as an internal standard.

Optimization of the Temperature[a]

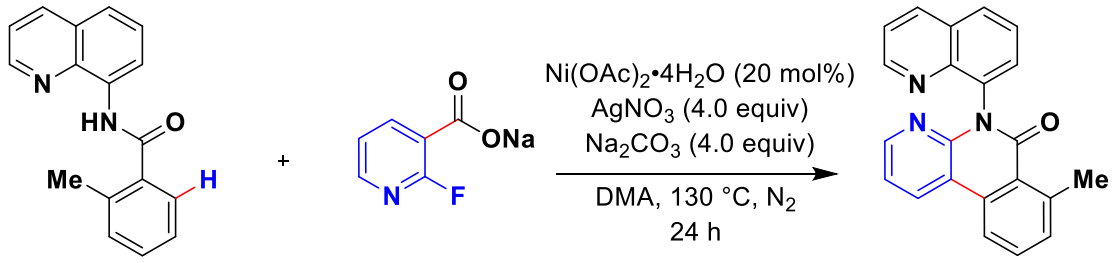


1a **4a** **5a**

entry	Temperature (°C)	yield **5a** (%)[b]
1	120	56
2	130	72
3	140	73
4	150	73

[a]Reaction conditions: **1a** (0.200 mmol), **4a** (0.300 mmol) in DMA (2 mL). [b]^{1}H NMR yield determined from integration using 1,3,5-trimethoxybenzene as an internal standard.

Equivalents of 4a[a]



1a **4a** **5a**

entry	**4a**	yield **5a** (%)[b]
1	1.5 equiv	73
2	2.0 equiv	81
3	3.0 equiv	81

[a]Reaction conditions: **1a** (0.200 mmol), **4a** in DMA (200 mL). [b]^{1}H NMR yield determined from integration using 1,3,5-trimethoxybenzene as an internal standard.

General Procedure for the Oxidative Decarboxylative Annulation Reaction

Procedure A: An oven-dried 50 mL Schlenk tube with a stirring bar was charged with carboxylic acid **4** (0.400 mmol), Na_2CO_3 (42.3 mg, 0.400 mmol), and dry DMA (1 mL). The reaction vessel was placed in a pre-heated oil bath and stirred for 0.5 h at 110 °C. The solvent was then removed under reduced pressure until dry and the carboxylate salt was used without further purification. The corresponding benzamide **1** (0.200 mmol), $Ni(OAc)_2•4H_2O$ (9.9 mg, 0.040 mmol), $AgNO_3$ (136 mg, 0.800 mmol), and Na_2CO_3 (84 mg, 0.80 mmol) were added and the tube was evacuated and backfilled with nitrogen three times after which dry DMA (2 mL) was added *via* syringe. The reaction mixture was stirred at 130 °C for 24 h. Upon completion, the reaction tube was cooled to room temperature. The solution was diluted with dichloromethane (30 mL) and filtered through a pad of celite. The celite was then washed with dichloromethane (2 x 30 mL). The solvent was removed by rotary evaporation (to ~2 mL) and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography (gradient elution, dichloromethane:ethyl acetate (19:1, v/v) to (7:1, v/v)), to yield the corresponding product.

Procedure B: An oven-dried 50 mL Schlenk tube with a stirring bar was charged with carboxylic acid **4** (0.400 mmol), Na_2CO_3 (42.3 mg, 0.400 mmol), and dry DMA (1 mL). The reaction vessel was placed in a pre-heated oil bath and stirred for 0.5 h at 110 °C. The solvent was then removed under reduced pressure until dry and the carboxylate salt was used without further purification. The corresponding benzamide **1** (0.200 mmol), $Ni(OAc)_2•4H_2O$ (9.9 mg, 0.040 mmol), $AgNO_3$ (136 mg, 0.800 mmol), and Na_2CO_3 (84 mg, 0.80 mmol) were added and the tube was evacuated and backfilled with nitrogen three times after which DMA (2 mL) was added *via* syringe. The reaction mixture was stirred at 170 °C for 24 h. Upon completion, the reaction tube was cooled to room temperature. The solution was diluted with dichloromethane (30 mL) and filtered through a pad of celite, the celite was washed with dichloromethane (2 x 30 mL). The solvent was removed by rotary evaporation (to ~2 mL) and concentrated under *vacuo*. The residue was purified by silica gel column chromatography (gradient elution, dichloromethane:ethyl acetate (19:1, v/v) to (7:1, v/v)), yielding the corresponding product.

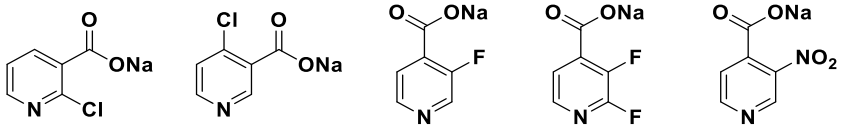
Procedure C: An oven-dried 50 mL Schlenk tube with a stirring bar was charged with carboxylic acid **4** (0.400 mmol), Na_2CO_3 (42.3 mg, 0.400 mmol), and dry DMA (1 mL). The reaction vessel was placed in a pre-heated oil bath and stirred for 0.5 h at 110 °C. The solvent was removed under reduced pressure until dry and the carboxylate salt was used without further purification. The corresponding benzamide **1** (0.200 mmol), $Ni(OAc)_2•4H_2O$ (9.9 mg, 0.040 mmol), $AgNO_3$ (136 mg, 0.800 mmol), Na_2CO_3 (84 mg, 0.80 mmol) were added and the tube was evacuated and backfilled with nitrogen three times after which DMA (2 mL) was added *via* syringe. The reaction mixture was stirred at 130 °C for 8h then 170 °C for 16h. Upon completion, the reaction tube was cooled to room temperature. The solution was diluted with dichloromethane (30 mL) and filtered through a pad of celite, the celite was washed with dichloromethane (2 x 30 mL). The solvent was removed by rotary evaporation (to ~2 mL) and concentrated under *vacuo*. The residue was purified by silica gel column chromatography (gradient elution,

dichloromethane:ethyl acetate (19:1, v/v) to (7:1, v/v)), yielding the corresponding product.

Procedure for the 1 mmol Scale Oxidative Decarboxylative Annulation Reaction. An oven-dried 100 mL Schlenk tube with a stirring bar was charged with 2-fluoronicotinic acid **4a** (282 mg, 2.00 mmol), Na_2CO_3 (212 mg, 2.00 mmol), and dry DMA (5 mL). The reaction vessel was placed in a pre-heated oil bath and stirred for 0.5 h at 110 °C. The solvent was removed under reduced pressure until dry and the carboxylate salt was used without further purification. The corresponding 2-methyl-N-(quinolin-8-yl) benzamide **1a** (262 mg, 1.00 mmol), $Ni(OAc)_2•4H_2O$ (49.7 mg, 0.20 mmol), $AgNO_3$ (679 mg, 4.00 mmol), Na_2CO_3 (424 mg, 4.00 mmol) were added and the tube was evacuated and backfilled with nitrogen three times after which DMA (10 mL) was added *via* syringe. The reaction mixture was stirred at 130 °C for 24 h. Upon completion, the reaction tube was cooled to room temperature. The solution was diluted with dichloromethane (50 mL) and filtered through a pad of celite, the celite was washed with dichloromethane (4 x 50 mL). The solvent was removed by rotary evaporation (to ~10 mL) and concentrated under *vacuo*. The residue was purified by silica gel column chromatography (gradient elution, dichloromethane:ethyl acetate (19:1, v/v) to (7:1, v/v)), yielding 253 mg (0.75 mmol) of the corresponding product in 75% yield.

Challenging Carboxylates

Heteroaromatic carboxylates that do not undergo decarboxylative arylation and cyclization under the standard reaction conditions.

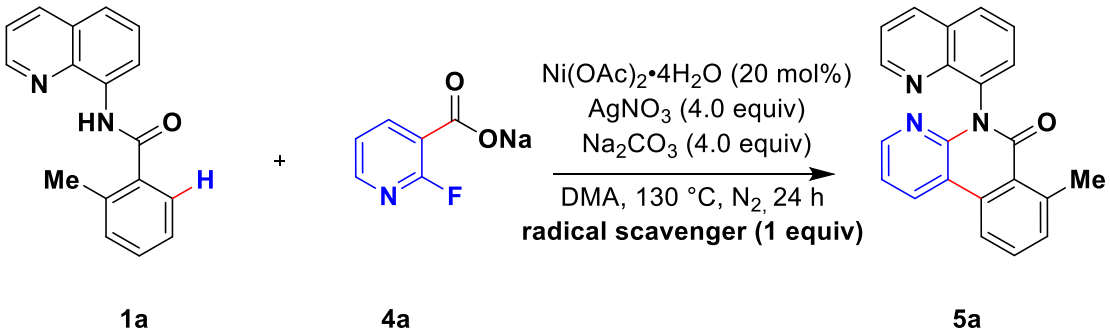


Mechanistic Studies

Control Reactions with Radical Scavengers.

An oven-dried 50 mL Schlenk tube with a stirring bar was charged with 2-fluoronicotinic acid **4a** (56.4 mg, 0.400 mmol), sodium carbonate (42.3 mg, 0.400 mmol), and dry DMA (1 mL). The reaction vessel was placed in a pre-heated oil bath and stirred for 0.5 h at 110 °C. The solvent was removed under reduced pressure until dry and the resulting carboxylate salt was used without further purification. 2-methyl-*N*-(quinolin-8-yl) benzamide **1a** (52.4 mg, 0.200 mmol), $Ni(OAc)_2 \bullet 4H_2O$ (9.9 mg, 0.040 mmol), $AgNO_3$ (136 mg, 0.800 mmol), Na_2CO_3 (84 mg, 0.80 mmol), and either TEMPO (31.2 mg, 0.200 mmol) or DHA (36.0, 0.200 mmol) were added. The tube was evacuated and backfilled with nitrogen three times after which DMA (2 mL) was added *via* syringe. The reaction mixture was stirred at 130 °C for 24 h. Upon completion, the reaction tube was cooled to room temperature. The solution was diluted with dichloromethane (30 mL) and filtered through a pad of celite. The celite was then washed with dichloromethane (2 x 30 mL). The solvent was concentrated by rotary evaporation (to ~2 mL) and the remaining solvent was removed under vacuum. A 1,3,5-trimethoxybenzene (5.00 mg) NMR standard was added to the residue and the crude mixture was dissolved in $CDCl_3$ for ^1H NMR analysis.

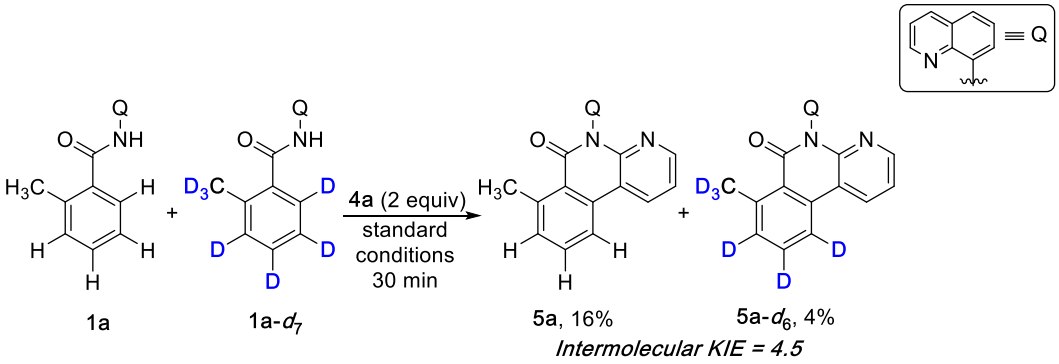
Control Reactions with Radical Scavengers[a]



entry	radical scavenger (1 equiv)	yield **5a** (%)[b]
1	none	81
2	TEMPO	74
3	DHA	78

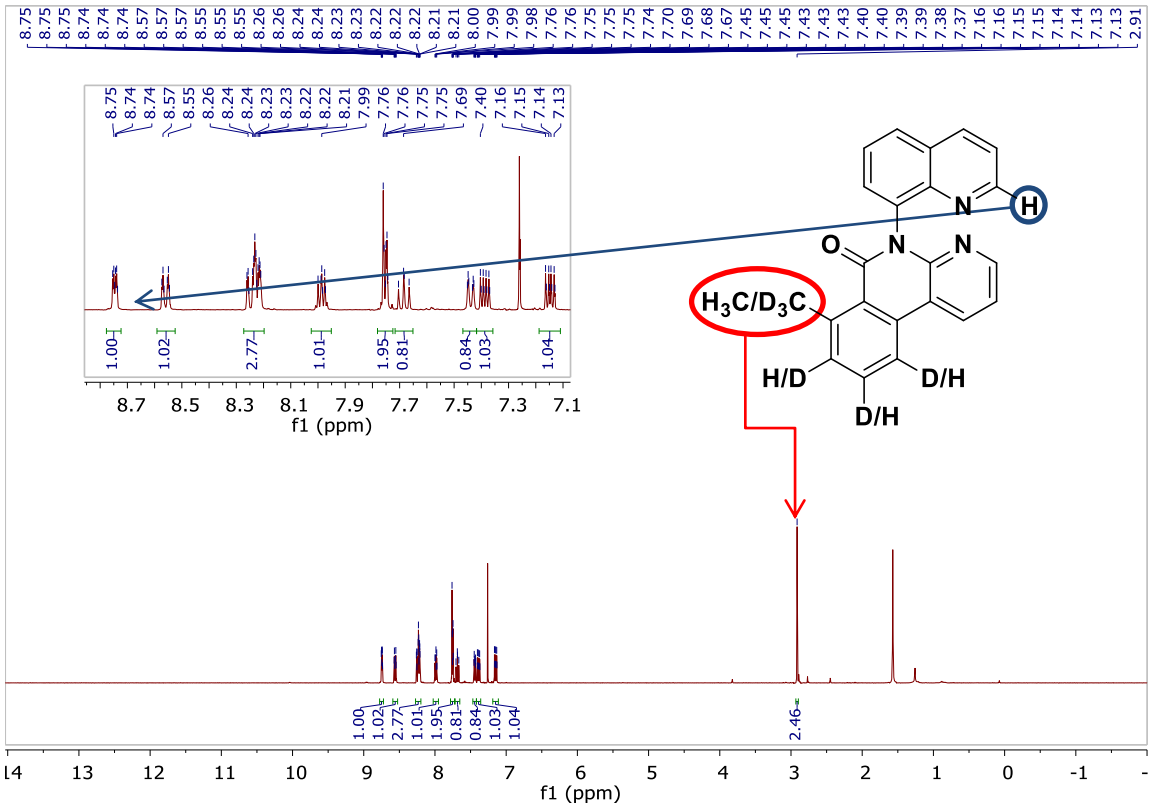
[a]Reaction conditions: **1a** (0.200 mmol), **4a** (0.400 mmol) in DMA (2 mL). [b]^{1}H NMR yield with 1,3,5-trimethoxybenzene as an internal standard.

Kinetic Isotope Effect Experiments

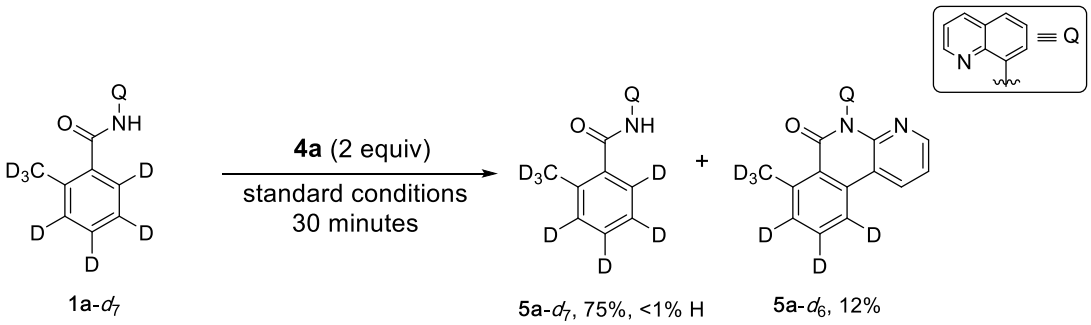


Procedure for the Intermolecular Competition Experiment. An oven-dried 50 mL Schlenk tube with a stirring bar was charged with 2-fluoronicotinic acid **4a** (56.4 mg, 0.400 mmol), sodium carbonate (42.3 mg, 0.400 mmol), and dry DMA (1 mL). The reaction vessel was placed in a pre-heated oil bath and stirred for 0.5 h at 110 °C. The solvent was removed under vacuum until dry and the resulting carboxylate salt was used without further purification. **1a** (26.2 mg, 0.100 mmol), 6-(methyl-d_3)-*N*-8-quinolinyl-benzamide-*2,3,4,5*-d_4 **1a-*d*$_7$** (26.9 mg, 0.100 mmol), $Ni(OAc)_2$•$4H_2O$ (9.9 mg, 0.040 mmol), $AgNO_3$ (136 mg, 0.800 mmol), Na_2CO_3 (84 mg, 0.80 mmol) were added, the tube

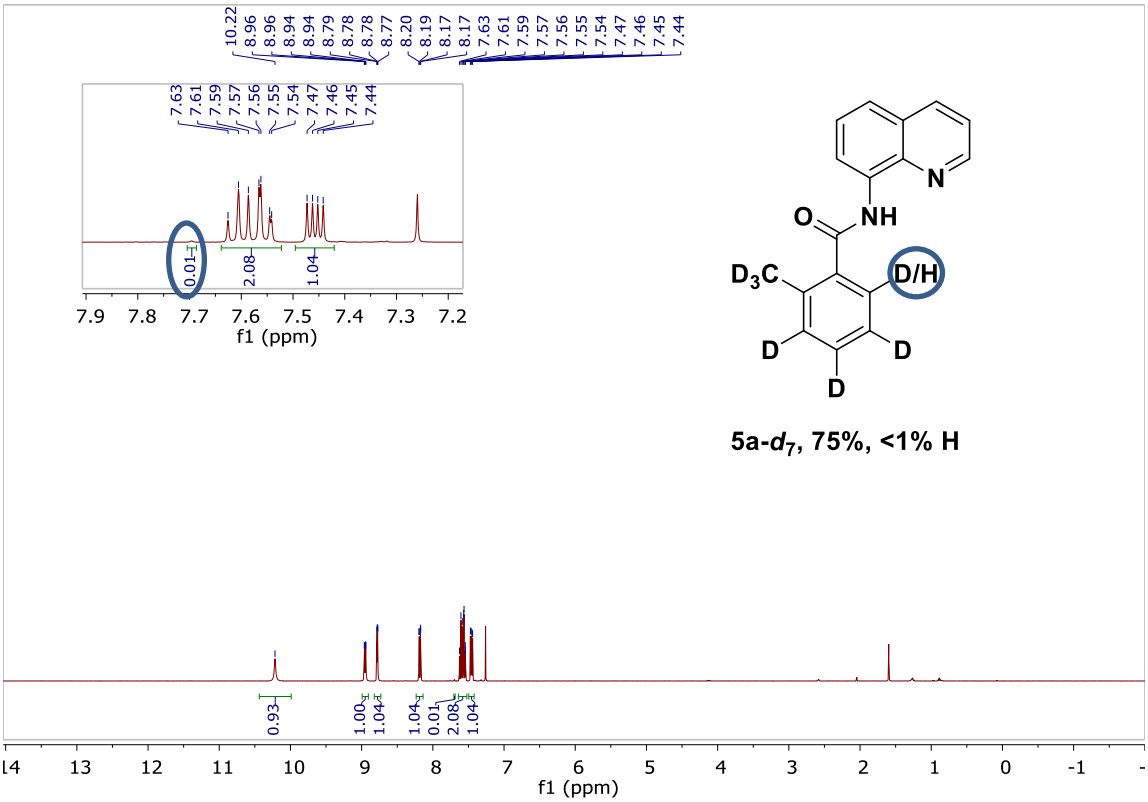
was evacuated and backfilled with nitrogen three times after which DMA (2 mL) was added *via* syringe. The reaction mixture was stirred at 130 °C for 30 minutes. Upon completion, the reaction tube was cooled to room temperature. The solution was diluted with dichloromethane (30 mL) and filtered through a pad of celite. The celite was then washed with dichloromethane (2 x 30 mL). The solvent was concentrated by rotary evaporation (to ~2 mL) and the remaining solvent was removed under vacuum. The resulting residue was purified by silica gel column chromatography (dichloromethane:ethyl acetate (19:1, v/v) to (7:1, v/v)), yielding the corresponding product as a mixture of **5a** and **5a-*d*$_6$** in 16% and 4% yields respectively (as determined by ^{1}H NMR spectroscopy), giving a KIE of 4.5.



Isotopic Exchange Experiment



Procedure for the Isotopic Exchange Experiment. An oven-dried 50 mL Schlenk tube with a stirring bar was charged with 2-fluoronicotinic acid **4a** (56.4 mg, 0.400 mmol), sodium carbonate (42.3 mg, 0.400 mmol), and dry DMA (1 mL). The reaction vessel was placed in a pre-heated oil bath and stirred for 0.5 h at 110 °C. The solvent was removed under reduced pressure until dry and the resulting carboxylate salt was used without further purification. **1a-*d*$_7$** (53.8 mg, 0.200mmol), $Ni(OAc)_2$•$4H_2O$ (9.9 mg, 0.040 mmol), $AgNO_3$ (136 mg, 0.800 mmol), and Na_2CO_3 (84 mg, 0.80 mmol) were added, the tube was evacuated and backfilled with nitrogen three times after which DMA (2 mL) was added *via* syringe. The reaction mixture was stirred at 130 °C for 30 minutes. Upon completion, the reaction tube was cooled to room temperature. The solution was diluted with dichloromethane (30 mL) and filtered through a pad of celite. The celite was then washed with dichloromethane (2 x 30 mL). The solvent was concentrated by rotary evaporation (to ~2 mL) and the remaining solvent removed under vacuum. The residue was purified by silica gel column chromatography (gradient elution, hexanes:ethyl acetate (9:1, v/v) to (4:1, v/v)), yielding the corresponding product. The extent of proton incorporation was determined to be 0.01H, less than 1%, by ^{1}H NMR spectroscopy.



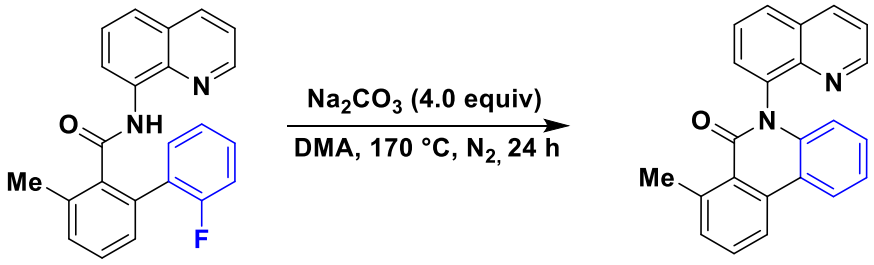
General Procedure for the Synthesis of (Hetero)Aryl Benzamides (1)

Procedure A: Synthesis from the Acid Chloride. A 100 mL two-neck round bottom flask was charged with 8-aminoquinoline (1.44 g, 10.0 mmol), Et_3N (1.53 mL, 11.0 mmol), and methylene chloride (20 mL) under a N_2 atmosphere. The corresponding acid chloride (12.0 mmol) was added dropwise at room temperature over 10 minutes. The mixture was stirred for 6 h at room temperature. The reaction was quenched with 10 mL of saturated $NaHCO_3$ and extracted with methylene chloride (3 x 25 mL). The combined organic layer was washed with brine (15 mL) and dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the residue was purified via silica gel column chromatography (gradient elution, hexanes : ethyl acetate (15:1, v/v) to (1:1, v/v)).

Procedure B: Synthesis from the carboxylic acid. A 50 mL two-neck round bottom flask was charged with the corresponding carboxylic acid (1.70 mmol), anhydrous *N*,*N*-dimethylformamide (2 drops), and methylene chloride (2 mL) under a N_2 atmosphere at 0

°C. Oxalyl chloride (0.17 mL, 2.00 mmol) was then added dropwise and the reaction mixture was allowed to stir for 3 h at room temperature. The solvent was removed under reduced pressure and the resulting acid chloride was used without further purification. A 100 mL two-neck round bottom flask was charged with 8-aminoquinoline (255 mg, 1.70 mmol), Et_3N (0.278 mL, 2.00 mmol), and methylene chloride (10 mL) under a N_2 atmosphere at 0 °C. The corresponding acid chloride was added dropwise to the reaction and stirred for 3 h. The reaction was quenched with 5 mL of saturated $NaHCO_3$ and extracted with methylene chloride three times (3 x 25 mL). The combined organic layer was washed with brine (15 mL) and dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the residue was purified via silica gel column chromatography (gradient elution, hexanes : ethyl acetate (19:1, v/v) to (9:1, v/v)).

Base Promoted Cyclization Reaction

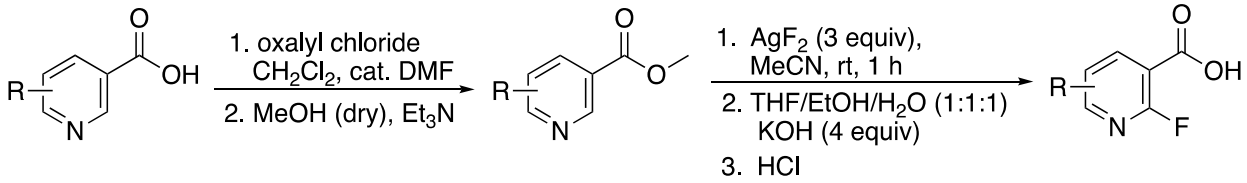


3r **5k, > 95%**

An oven-dried 50 mL Schlenk tube with a stirring bar was charged with 2'-fluoro-3-methyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide[66] (71.2 mg, 0.200 mmol) and Na_2CO_3 (84 mg, 0.80 mmol). The tube was evacuated and backfilled with nitrogen three times after which DMA (2 mL) was added *via* syringe. The reaction mixture was stirred at 170 °C for 24 h. Upon completion, the reaction tube was cooled to room temperature. The solution was diluted with dichloromethane (30 mL) and filtered through a pad of celite, the celite was washed with dichloromethane (2 x 30 mL). The solvent was concentrated by rotary evaporation (to ~2 mL) and the remaining solvent was removed under vacuum. Then 1,3,5-trimethoxybenzene (5.00 mg) was added to the residue and the crude mixture was dissolved in $CDCl_3$ for analysis by ^1H NMR spectroscopy.

General Procedures for the Synthesis of Fluorinated Carboxylic Acids (4)

Procedure A:Synthesis from Silver(II) Fluoride

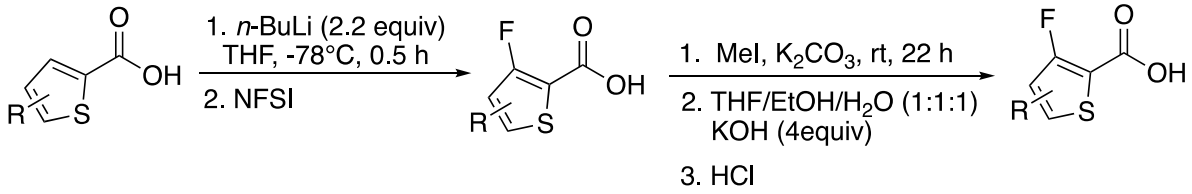


Synthesis of methyl esters. A 50 mL two-neck round bottom flask was charged with the corresponding carboxylic acid (3.62 mmol), *N*,*N*-dimethylformamide (3-4 drops), and methylene chloride (4 mL) under a N_2 atmosphere at 0 °C. Oxalyl chloride (0.32 mL, 3.8 mmol) was then added dropwise and the reaction mixture was allowed to stir for 3 h at room temperature after removal of the ice bath. The solvent was removed under reduced pressure and anhydrous methanol was then added to the resulting crude acid chloride. Triethylamine (0.55 mL, 4.00 mmol) was added dropwise to the mixture and the reaction was allowed to stir for 3 h. The reaction was quenched with saturated $NaHCO_3$ (5 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the residue was purified via silica gel column chromatography (gradient elution, hexanes : ethyl acetate (19:1, v/v) to (9:1, v/v) or (gradient elution, hexanes : dichloromethane (15:1, v/v) to (1:1, v/v).

Fluorination of heteroaryl methyl esters. The title compounds were prepared according to a literature procedure.[67] In a N_2 filled glovebox, the pyridine substrate (1.00 mmol) and anhydrous MeCN (20 mL) were combined in an oven-dried round bottom flask. While rapidly stirring, AgF_2 (438 mg, 3.00 mmol) was added at once. The round bottom flask was capped with a rubber septum and stirred for 1 hour. The reaction mixture was then removed from the glovebox and poured into a separatory funnel containing 40 mL of saturated aqueous $NaHCO_3$ and the mixture extracted with Et_2O (2 x 30 mL). The organic layer was washed with brine (40 mL) and dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the residue was purified via silica gel column chromatography.

Hydrolysis of fluorinated heteroaryl methyl esters. A 100 mL round bottom flask was charged with the fluorinated heteroaryl methyl ester (1.0 mmol), THF/EtOH/H_2O (1:1:1, 2 mL/2 mL/2 mL), and KOH (4 equiv). The mixture was monitored by TLC until all starting material was consumed. The reaction was acidified with HCl (2 N) until a pH of 2 was achieved. The reaction mixture was poured into a separatory funnel and extracted with ethyl acetate (3 x 50 mL) and dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the resulting acid was used without further purification.

Procedure B: Synthesis from Lithiation and Fluorination with NFSI



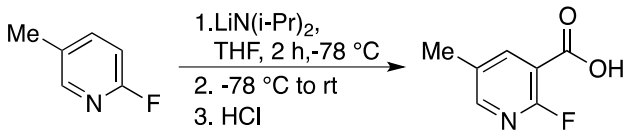
Fluorination of 2-thiophenecarboxylic acid substrates. The title compounds were prepared following a procedure modified from the literature.[68] To a pre-cooled (-78 °C) solution of 2-thiophenecarboxylic acid substrate (5.61 mmol) in anhydrous THF (25 mL) was added *n*-BuLi (4.93 mL, 12.3 mmol) dropwise. After the reaction stirred for 30 minutes, a solution of *N*-fluorobenzenesulfonimide (NFSI, 2.65 g, 8.41 mmol) in anhydrous THF (22 mL) was added dropwise at -78 °C. The solution was stirred at -78°C for 5 hours and then warmed slowly and allowed to stir at room temperature overnight. The reaction was quenched with 6 N HCl (3 mL) at 0 °C. The reaction mixture was poured into a separatory funnel and extracted with ethyl acetate (3 x 75 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude solid was then dissolved in a mixture of a minimum amount of water (~150mL) and NaOH (1.2 equiv). The aqueous layer was poured into a separatory funnel and washed with dichloromethane until all residual NFSI was removed. The aqueous layer was then acidified with HCl (2 N) until a pH of 2 was achieved. The reaction mixture was poured into a separatory funnel and extracted with ethyl acetate (3 x 75 mL) and dried over

anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure to yield the crude fluorinated thiophenecarboxylic acid which was used as described below without further purification.

Methylation of 2-thiophenecarboxylic acid substrates. To an oven-dried round bottom flask was charged the crude fluorinated thiophenecarboxylic acid, K_2CO_3(1.07 g, 7.74 mmol), anhydrous DMF (10 mL), and methyl iodide (0.70 mL, 11.2 mmol). The reaction mixture was stirred at room temperature for 22 hours. After completion, saturated ammonium chloride (15 mL) was added and the resulting mixture was extracted with ethyl acetate (3 x 50 mL). The organic phase was washed with water (100 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The residue was purified via silica gel column chromatography to give the corresponding methyl ester.

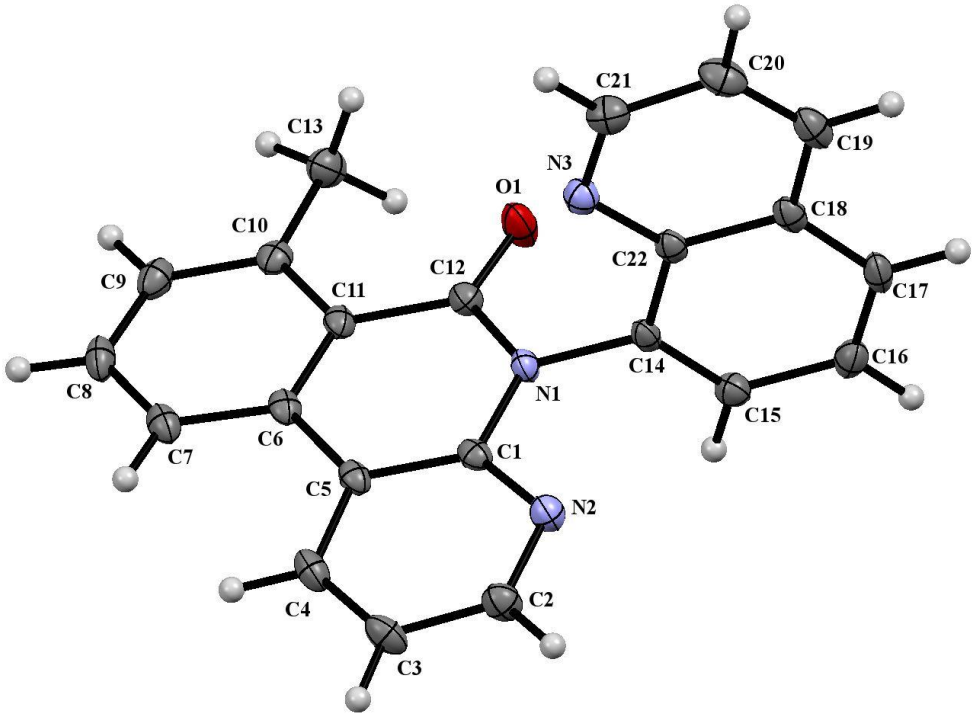
Hydrolysis of fluorinated methyl 2-thiophenecarboxylate. A 100 mL round bottom flask was charged with the fluorinated methyl 2-thiophenecarboxylate (2.0 mmol), THF/EtOH/H_2O (1:1:1, 4 mL/4 mL/4 mL)), and KOH (4 equiv). The mixture was monitored by TLC until all starting material was consumed. The reaction was acidified with HCl (2 N) until a pH of 2 was achieved. The reaction mixture was poured into a separatory funnel and extracted with ethyl acetate (3 x 50 mL) and dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure and used without further purification.

Procedure C: Synthesis from Lithiation and Carboxylation



Carboxylation of 2-fluoro-5-methylpyridine: The title compound was prepared following a modification of a literature synthesis.[69] A 2.5 M solution of *n*-butyl lithium in hexanes (2.28 mL, 5.70 mmol) was added dropwise to a solution of freshly distilled

diisopropylamine (0.80 mL, 5.70 mmol) in THF (10 mL) at -78 °C. After complete addition, the mixture was allowed to warm to 0 °C and stir at this temperature for 10 minutes. The solution was then cooled back down to -78 °C and a solution of 2-fluoro-5-methylpyridine (0.59 mL, 5.70 mmol) in THF (1.85 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 2 hours and then quenched with freshly made dry ice (~1 brick). The reaction mixture was allowed to warm to room temperature and was then acidified with HCl (2 N) until a pH of 2 was achieved and extracted with ethyl acetate (3 x 50 mL). The organic phase was washed with brine (20 mL) and dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure.



Perspective view of the molecular structure of the $C_{22}H_{15}N_3O$ (**5a**) with the atom labeling scheme for the non-hydrogen atoms. Thermal ellipsoids are scaled to enclose 50% probability.

Description of the X-ray Structural Analysis of $C_{22}H_{15}N_3O$ (5a).

A colorless rectangular crystal of $C_{22}H_{15}N_3O$ (**5a**) was covered in a polybutene oil (Sigma-Aldrich) and placed on the end of a MiTeGen loop. The sample was cooled to

100 K with an Oxford Cryostream 700 system and optically aligned on a Bruker AXS D8 Venture fixed-chi X-ray diffractometer equipped with a Triumph monochromator, a Mo Kα radiation source (λ = 0.71073 Å), and a PHOTON 100 CMOS detector. Three sets of 12 frames each were collected using the omega scan method with a 10 s exposure time. Integration of these frames followed by reflection indexing and least-squares refinement produced a crystal orientation matrix for the monoclinic crystal lattice that was used for the structural analysis.

Data collection consisted of the measurement of a total of 246 frames in two runs using omega scans with the detector held at 5.00 cm from the crystal. Frame scan parameters are summarized in Table 1 below:

Data collection details for $C_{22}H_{15}N_3O$ (5a).

Run	2θ	ω	φ	χ	Scan Width (°)	Frames	Exposure Time (sec)
1	17.45	-164.74	-217.75	54.78	1.50	123	40.00
2	17.45	-164.74	45.40	54.78	1.50	123	40.00

The APEX3 software program (version 2016.9-0)[100] was used for diffractometer control, preliminary frame scans, indexing, orientation matrix calculations, least-squares refinement of cell parameters, and the data collection. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 14343 reflections to a maximum θ angle of 27.50° (0.77 Å resolution), of which 3597 were independent (average redundancy 3.987, completeness = 99.8%, R_{int} = 3.31%, R_{sig} = 3.09%) and 2792 (77.62%) were greater than $2\sigma(F^2)$. The final cell constants of a = 13.4326(7) Å, b = 7.3348(4) Å, c = 17.1068(9) Å, β = 111.9152(15)°, volume = 1563.66(14) $Å^3$, are based

upon the refinement of the XYZ-centroids of 6729 reflections above 20 σ(I) with 6.445° < 2θ < 60.15°. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.809. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.962 and 0.992.

The structure was solved by direct methods and difference Fourier analysis using the programs provided by SHELXL-2014/7.[101] Idealized positions for the hydrogen atoms were included as fixed contributions using a riding model with isotropic temperature factors set at 1.2 (aromatic hydrogens) or 1.5 times (methyl hydrogens) that of the adjacent carbon atom. The positions of the methyl hydrogen atoms were optimized by a rigid rotating group refinement with idealized angles. Full-matrix least-squares refinement, based upon the minimization of $\Sigma w_i |F_o^2 - F_c^2|^2$, with weighting $w_i^{-1} = [\sigma^2(F_o^2) + (0.0524\ P)^2 + 0.7107\ P]$, where $P = (\text{Max}\ (F_o^2, 0) + 2\ F_c^2)/3$.[101] The final anisotropic full-matrix least-squares refinement on F^2 with 236 variables converged at R1 = 3.99%, for the 2792 observed data with I>2σ(I) and wR2 = 11.05% for all data. The value of the goodness-of-fit was 1.019.[102] The linear absorption coefficient, atomic scattering factors, and anomalous dispersion corrections were calculated from values found in the International Tables of X-ray Crystallography.[103]

Crystal data for $C_{22}H_{15}N_3O$ (5a).

Ident. code	jh43cms
Chemical form.	$C_{22}H_{15}N_3O$
Formula wght.	337.37 g/mol
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal size	0.086 x 0.277 x 0.432 mm
Crystal system	monoclinic

Space group	$P2_1/c$ (No. 14)	
Unit cell	a = 13.4326(7) Å	α = 90°
	b = 7.3348(4) Å	β = 111.9152(15)°
	c = 17.1068(9) Å	γ = 90°
Volume, $Å^3$	1563.66(14)	
Z	4	
Density (calc)	1.433 g/cm^3	
Abs. coefficient	0.090 mm^{-1}	
F(000)	704	

Data collection and structure refinement for $C_{22}H_{15}N_3O$ (5a).

Theta range	3.06 to 27.50°	
Index ranges	$-17 \leq h \leq 17$, $-9 \leq k \leq 8$, $-17 \leq l \leq 22$	
Reflections	14343	
Independent refls	3597 [R(int) = 0.0331]	
Coverage	99.8%	
Absorption correction	multi-scan	
Max. and min. trans.	0.992 and 0.962	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2014/7 (Sheldrick, 2014)	
Data / restraints / parameters	3597 / 0 / 236	
Goodness-of-fit on F^2	1.019	
Final R indices	2792 data; $I>2\sigma(I)$	R1 = 0.0399, wR2 = 0.0986
	all data	R1 = 0.0576, wR2 = 0.1105

Largest diff. peak and hole	0.325 and -0.256 $e^-/Å^3$

Atomic coordinates and equivalent isotropic atomic displacement parameters ($Å^2$) for $C_{22}H_{15}N_3O$ (5a). U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U(eq)
O1	0.13435(8)	0.87131(16)	0.22197(6)	0.0267(3)
N1	0.21961(8)	0.76163(16)	0.14127(7)	0.0147(2)
N2	0.31986(9)	0.66240(16)	0.06551(7)	0.0184(3)
N3	0.27078(9)	0.45464(16)	0.24227(7)	0.0181(3)
C1	0.22280(10)	0.70165(18)	0.06493(8)	0.0148(3)
C2	0.32566(12)	0.6120(2)	0.99213(9)	0.0208(3)
C3	0.23747(12)	0.5973(2)	0.91781(9)	0.0217(3)
C4	0.13755(12)	0.63391(19)	0.91951(9)	0.0200(3)
C5	0.12687(11)	0.68863(18)	0.99396(8)	0.0154(3)
C6	0.02538(10)	0.73730(18)	0.00170(8)	0.0154(3)
C7	0.92732(11)	0.71797(19)	0.93335(9)	0.0192(3)
C8	0.83324(11)	0.7707(2)	0.94140(9)	0.0217(3)
C9	0.83429(11)	0.84533(19)	0.01598(9)	0.0209(3)
C10	0.92885(11)	0.86398(19)	0.08593(8)	0.0176(3)
C11	0.02545(10)	0.80637(18)	0.07850(8)	0.0157(3)
C12	0.12732(11)	0.81760(19)	0.15249(8)	0.0166(3)
C13	0.92210(12)	0.9441(2)	0.16473(9)	0.0240(3)

	x/a	y/b	z/c	U(eq)
C14	0.31676(10)	0.75799(19)	0.21557(8)	0.0150(3)
C15	0.38375(11)	0.9038(2)	0.23626(8)	0.0182(3)
C16	0.47808(11)	0.9018(2)	0.31006(9)	0.0203(3)
C17	0.50156(11)	0.7527(2)	0.36117(8)	0.0192(3)
C18	0.43384(11)	0.59807(19)	0.34117(8)	0.0169(3)
C19	0.45540(12)	0.4381(2)	0.39002(9)	0.0223(3)
C20	0.38625(12)	0.2948(2)	0.36578(9)	0.0248(3)
C21	0.29503(12)	0.3093(2)	0.29094(9)	0.0220(3)
C22	0.33916(10)	0.59981(19)	0.26677(8)	0.0151(3)

Interatomic distances (Å) for $C_{22}H_{15}N_3O$ (5a).

O1-C12	1.2219(16)	N1-C12	1.3855(17)
N1-C1	1.3939(16)	N1-C14	1.4426(16)
N2-C1	1.3315(17)	N2-C2	1.3385(17)
N3-C21	1.3167(18)	N3-C22	1.3660(18)
C1-C5	1.4056(18)	C2-C3	1.381(2)
C3-C4	1.380(2)	C4-C5	1.3930(19)
C5-C6	1.4623(19)	C6-C7	1.4044(18)
C6-C11	1.4079(19)	C7-C8	1.377(2)
C8-C9	1.383(2)	C9-C10	1.3890(19)
C10-C11	1.4147(19)	C10-C13	1.504(2)
C11-C12	1.4792(18)	C14-C15	1.357(2)
C14-C22	1.4168(19)	C15-C16	1.4162(19)
C16-C17	1.362(2)	C17-C18	1.414(2)
C18-C19	1.406(2)	C18-C22	1.4244(18)

C19-C20	1.361(2)	C20-C21	1.407(2)

Bond **angles (°) for $C_{22}H_{15}N_3O$ (5a)**.

C12-N1-C1	124.42(11)	C12-N1-C14	116.45(10)
C1-N1-C14	119.05(11)	C1-N2-C2	116.89(11)
C21-N3-C22	117.24(12)	N2-C1-N1	115.71(11)
N2-C1-C5	124.83(12)	N1-C1-C5	119.46(12)
N2-C2-C3	123.69(13)	C4-C3-C2	118.19(13)
C3-C4-C5	120.56(13)	C4-C5-C1	115.80(12)
C4-C5-C6	124.81(12)	C1-C5-C6	119.37(12)
C7-C6-C11	119.15(12)	C7-C6-C5	121.09(12)
C11-C6-C5	119.76(11)	C8-C7-C6	119.93(13)
C7-C8-C9	120.64(13)	C8-C9-C10	121.65(13)
C9-C10-C11	117.89(13)	C9-C10-C13	117.96(13)
C11-C10-C13	124.15(12)	C6-C11-C10	120.67(12)
C6-C11-C12	119.78(12)	C10-C11-C12	119.55(12)
O1-C12-N1	118.81(12)	O1-C12-C11	124.14(12)
N1-C12-C11	117.05(11)	C15-C14-C22	121.14(12)
C15-C14-N1	120.59(12)	C22-C14-N1	118.26(12)
C14-C15-C16	120.64(13)	C17-C16-C15	119.79(13)
C16-C17-C18	120.99(12)	C19-C18-C17	123.65(12)
C19-C18-C22	117.10(13)	C17-C18-C22	119.24(12)
C20-C19-C18	119.83(13)	C19-C20-C21	118.84(14)
N3-C21-C20	124.22(14)	N3-C22-C14	119.03(12)
N3-C22-C18	122.76(12)	C14-C22-C18	118.20(12)

Anisotropic atomic displacement parameters ($Å^2$) for $C_{22}H_{15}N_3O$ (5a).

The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$.

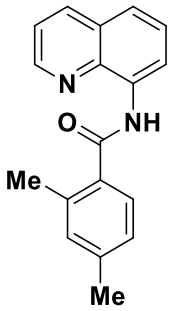
	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	0.0199(5)	0.0430(7)	0.0154(5)	-0.0053(5)	0.0044(4)	0.0042(5)
N1	0.0130(5)	0.0176(6)	0.0110(5)	0.0010(4)	0.0015(4)	0.0010(4)
N2	0.0179(6)	0.0206(6)	0.0156(6)	-0.0006(5)	0.0049(5)	0.0017(5)
N3	0.0182(6)	0.0191(6)	0.0168(6)	-0.0019(5)	0.0062(5)	-0.0006(5)
C1	0.0181(6)	0.0121(6)	0.0135(6)	0.0016(5)	0.0052(5)	0.0005(5)
C2	0.0211(7)	0.0236(7)	0.0185(7)	-0.0005(6)	0.0083(6)	0.0036(6)
C3	0.0289(8)	0.0218(7)	0.0140(7)	-0.0013(5)	0.0075(6)	0.0048(6)
C4	0.0238(7)	0.0173(7)	0.0133(6)	-0.0003(5)	0.0007(5)	0.0016(6)
C5	0.0181(6)	0.0124(6)	0.0130(6)	0.0018(5)	0.0027(5)	0.0001(5)
C6	0.0168(6)	0.0107(6)	0.0155(6)	0.0030(5)	0.0022(5)	0.0006(5)
C7	0.0216(7)	0.0151(7)	0.0158(6)	0.0005(5)	0.0013(5)	-0.0017(6)
C8	0.0162(6)	0.0190(7)	0.0216(7)	0.0027(6)	-0.0023(5)	-0.0016(6)
C9	0.0150(6)	0.0188(7)	0.0271(8)	0.0047(6)	0.0058(6)	0.0007(6)
C10	0.0167(6)	0.0150(6)	0.0205(7)	0.0045(5)	0.0061(5)	0.0003(5)
C11	0.0154(6)	0.0141(6)	0.0148(6)	0.0034(5)	0.0024(5)	-0.0006(5)
C12	0.0165(6)	0.0175(7)	0.0151(6)	0.0010(5)	0.0049(5)	0.0001(5)
C13	0.0187(7)	0.0307(8)	0.0229(7)	0.0034(6)	0.0083(6)	0.0044(6)
C14	0.0130(6)	0.0212(7)	0.0103(6)	-0.0017(5)	0.0039(5)	0.0019(5)
C15	0.0192(7)	0.0202(7)	0.0155(6)	-0.0001(5)	0.0069(5)	0.0001(6)
C16	0.0166(7)	0.0247(7)	0.0203(7)	-0.0063(6)	0.0076(6)	-0.0043(6)
C17	0.0134(6)	0.0283(8)	0.0133(6)	-0.0047(6)	0.0019(5)	0.0013(6)

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C18	0.0157(6)	0.0227(7)	0.0125(6)	-0.0019(5)	0.0054(5)	0.0041(6)
C19	0.0209(7)	0.0292(8)	0.0149(7)	0.0001(6)	0.0045(5)	0.0083(6)
C20	0.0319(8)	0.0212(7)	0.0224(7)	0.0057(6)	0.0115(6)	0.0070(6)
C21	0.0248(7)	0.0196(7)	0.0236(7)	-0.0006(6)	0.0115(6)	0.0003(6)
C22	0.0150(6)	0.0187(7)	0.0120(6)	-0.0017(5)	0.0056(5)	0.0018(5)

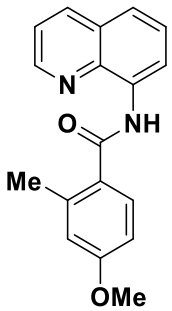
Hydrogen atom coordinates and isotropic atomic displacement parameters ($Å^2$) for $C_{22}H_{15}N_3O$ (5a).

	x/a	y/b	z/c	U(eq)
H2	0.3943	0.5848	-0.0089	0.025
H3	0.2454	0.5629	-0.1331	0.026
H4	0.0755	0.6217	-0.1305	0.024
H7	-0.0741	0.6685	-0.1184	0.023
H8	-0.2330	0.7558	-0.1047	0.026
H9	-0.2313	0.8848	0.0194	0.025
H13A	-0.1504	0.9916	0.1524	0.036
H13B	-0.0257	1.0434	0.1850	0.036
H13C	-0.0620	0.8495	0.2081	0.036
H15	0.3672	1.0083	0.2009	0.022
H16	0.5248	1.0041	0.3239	0.024
H17	0.5644	0.7526	0.4110	0.023
H19	0.5181	0.4301	0.4398	0.027
H20	0.3993	0.1869	0.3988	0.03
H21	0.2479	0.2077	0.2745	0.026

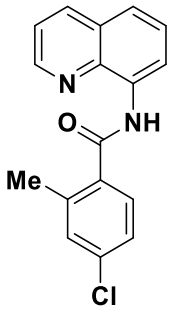
Characterization of (Hetero)Aryl Benzamides (1)



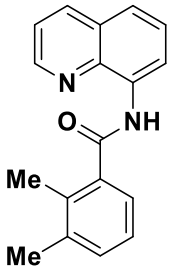
2,4-dimethyl-*N*-(quinolin-8-yl)benzamide (1q). The title compound was synthesized following General Procedure B. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.22 (s, 1H), 8.94 (dd, *J* = 7.5, 1.5 Hz, 1H), 8.77 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.65 – 7.57 (m, 2H), 7.54 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.18 – 7.09 (m, 2H), 2.59 (s, 3H), 2.39 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ = 168.22, 148.25, 140.55, 138.65, 136.88, 136.35, 134.91, 133.76, 132.25, 128.03, 127.46, 127.45, 126.69, 121.66, 121.66, 116.42, 21.37, 20.34. The spectral data are consistent with those reported in the literature.[70]



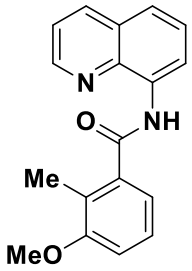
4-methoxy-2-methyl-*N*-(quinolin-8-yl)benzamide (1r). The title compound was synthesized following General Procedure B. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.21 (s, 1H), 8.92 (dd, *J* = 7.5, 1.5 Hz, 1H), 8.79 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.72 – 7.67 (m, 1H), 7.59 (dd, *J* = 8.3, 7.5 Hz, 1H), 7.54 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.46 (dd, *J* = 8.2, 4.2 Hz, 1H), 6.88 – 6.81 (m, 2H), 3.87 (s, 3H), 2.62 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ = 167.82, 161.10, 148.26, 139.47, 138.69, 136.41, 135.01, 129.33, 129.04, 128.07, 127.50, 121.69, 121.57, 117.01, 116.38, 111.12, 55.39, 20.91. The spectral data are consistent with those reported in the literature.[70]



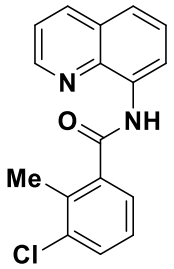
4-chloro-2-methyl-*N*-(quinolin-8-yl)benzamide (1s). The title compound was synthesized following General Procedure B. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.19 (s, 1H), 8.91 (dd, *J* = 7.3, 1.7 Hz, 1H), 8.78 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.66 – 7.54 (m, 3H), 7.47 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.33 – 7.28 (m, 2H), 2.59 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 167.10, 148.38, 138.90, 138.57, 136.44, 136.15, 134.99, 134.55, 131.33, 128.69, 128.03, 127.42, 126.21, 122.03, 121.78, 116.60, 20.21. The spectral data are consistent with those reported in the literature.[70]



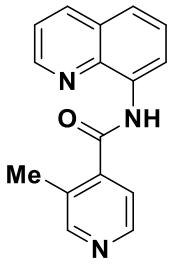
2,3-dimethyl-*N*-(quinolin-8-yl)benzamide (1u). The title compound was synthesized following General Procedure B. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.13 (s, 1H), 8.96 (dd, *J* = 7.5, 1.5 Hz, 1H), 8.76 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.65 – 7.53 (m, 2H), 7.51 – 7.42 (m, 2H), 7.29 (d, *J* = 7.0 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 2.46 (s, 3H), 2.36 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 168.97, 148.22, 138.51, 138.10, 137.57, 136.28, 134.74, 134.56, 131.55, 127.95, 127.34, 125.70, 124.71, 121.77, 121.63, 116.46, 20.36, 16.50. The spectral data are consistent with those reported in the literature.[71]



3-methoxy-2-methyl-*N*-(quinolin-8-yl)benzamide (1t). The title compound was synthesized following General Procedure B. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.15 (s, 1H), 8.95 (dd, *J* = 7.6, 1.5 Hz, 1H), 8.76 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.65 – 7.51 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.34 – 7.22 (m, 2H), 6.98 (dd, *J* = 7.9, 1.5 Hz, 1H), 3.89 (s, 3H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 168.28, 158.23, 148.29, 138.58, 138.43, 136.35, 134.73, 128.01, 127.41, 126.84, 125.17, 121.84, 121.70, 119.12, 116.53, 111.81, 55.75, 12.88. The spectral data are consistent with those reported in the literature.[71]

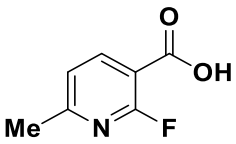


3-chloro-2-methyl-*N*-(quinolin-8-yl)benzamide (1v). The title compound was synthesized following General Procedure B as a white solid in 58% yield (293 mg, 0.98 mmol), mp = 161 – 163 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.14 (s, 1H), 8.93 (dd, *J* = 7.2, 1.8 Hz, 1H), 8.77 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.66 – 7.42 (m, 5H), 7.26 (t, *J* = 7.8 Hz, 1H), 2.59 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 167.45, 148.42, 139.12, 138.56, 136.46, 136.09, 134.47, 134.43, 131.03, 128.05, 127.42, 127.07, 125.53, 122.19, 121.82, 116.74, 17.29. FTIR (ATR, cm^{-1}): 3359, 3061, 1674, 1527, 1486, 1427, 1382, 1329, 788, 663. HRMS (ESI-MS) m/z calcd for $C_{17}H_{14}ClN_2O$ $[M + H]^+$ 297.0794 found 297.0793.

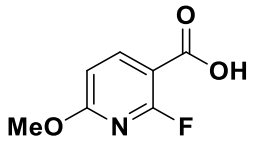


3-methyl-*N*-(quinolin-8-yl)pyridine-4-carboxamide (1x). The title compound was synthesized following General Procedure B. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.27 (s, 1H), 8.91 (dd, *J* = 6.3, 2.7 Hz, 1H), 8.80 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.62 (d, *J* = 1.0 Hz, 2H), 8.20 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.66 – 7.57 (m, 2H), 7.54 (d, *J* = 5.0 Hz, 1H), 7.48 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.59 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.70, 152.53, 148.52, 148.06, 143.03, 138.52, 136.49, 134.11, 130.84, 128.02, 127.36, 122.47, 121.90, 120.73, 116.86, 17.05. The spectral data are consistent with those reported in the literature.[70]

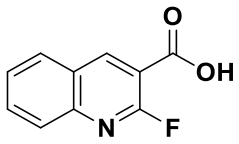
Characterization of *ortho*-Fluoro Heteroaromatic Carboxylic Acids (4)



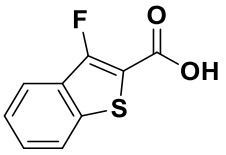
2-fluoro-6-methylpyridine-3-carboxylic acid (4b). The title compound was synthesized following Procedure A for the Synthesis of Fluorinated Carboxylic Acids as a white solid in 91 % yield, mp = 182 – 184 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.40 (s, 1H), 8.25 (dd, *J* = 9.9, 7.7 Hz, 1H), 7.30 (dd, *J* = 7.8, 1.8 Hz, 1H), 2.47 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 164.08 (d, *J* = 7.7 Hz), 161.91 (d, *J* = 15.1 Hz), 160.26 (d, *J* = 245.6 Hz), 143.58 (d, *J* = 1.8 Hz), 121.43 (d, *J* = 4.6 Hz), 110.92 (d, *J* = 24.8 Hz), 23.56. ^{19}F NMR (376 MHz, DMSO-d_6): δ = -64.43 (d, *J* = 10.0 Hz). FTIR (ATR, cm^{-1}): 2918, 2592, 1725, 1616, 1478, 1243, 1215, 1083, 779, 726. HRMS (ESI-MS) m/z calcd for $C_7H_7FNO_2$ $[M + H]^+$ 156.0460 found 156.0458.



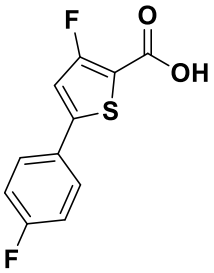
2-fluoro-6-methoxypyridine-3-carboxylic acid (4c). The title compound was synthesized following Procedure A for the Synthesis of Fluorinated Carboxylic Acids as a white solid in 33% yield, mp = 210 – 212 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.18 (s, 1H), 8.24 (dd, *J* = 9.8, 8.4 Hz, 1H), 6.81 (dd, *J* = 8.4, 1.0 Hz, 1H), 3.88 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 165.18 (d, *J* = 14.5 Hz), 163.87 (d, *J* = 7.6 Hz), 160.67 (d, *J* = 251.0 Hz), 145.45 (d, *J* = 1.9 Hz), 107.79 (d, *J* = 5.1 Hz), 105.27 (d, *J* = 22.4 Hz), 54.60. ^{19}F NMR (376 MHz, DMSO-d_6): δ -63.13 (d, *J* = 9.8 Hz). FTIR (ATR, cm^{-1}): 2962, 2571, 1670, 1610, 1499, 1412, 1399, 1303, 1144, 1017, 930, 847, 789. HRMS (ESI-MS) m/z calcd for$C_7H_7FNO_3$ $[M + H]^+$ 172.0409 found 172.0406.



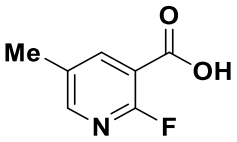
2-fluoroquinoline-3-carboxylic acid (4h). The title compound was synthesized following Procedure A at 50 °C for Synthesis of Fluorinated Carboxylic Acids as a white solid in 73% yield, mp = 258 – 260 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.65 (s, 1H), 9.12 (d, *J* = 9.8 Hz, 1H), 8.23 (d, *J* = 8.1 Hz, 1H), 7.92 (dd, *J* = 4.5, 1.1 Hz, 2H), 7.70 (dt, *J* = 8.2, 3.9 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 163.91 (d, *J* = 7.5 Hz), 157.75 (d, *J* = 247.6 Hz), 146.19 (d, *J* = 17.5 Hz), 145.72 (d, *J* = 4.0 Hz), 133.03, 129.30, 127.10 (d, *J* = 1.5 Hz), 127.00 (d, *J* = 2.3 Hz), 126.14 (d, *J* = 2.3 Hz), 114.43 (d, *J* = 30.8 Hz). ^{19}F NMR (376 MHz, DMSO-d_6): δ = -56.49 (d, *J* = 9.5 Hz). FTIR (ATR, cm^{-1}): 2971, 2585, 1695, 1620, 1601, 1472, 1417, 1264, 1078, 915, 788, 750. HRMS (ESI-MS) m/z calcd for $C_{10}H_7FNO_2$ $[M + H]^+$ 192.0460 found 192.0458.



3-fluoro-1-benzothiophene-2-carboxylic acid (4i). The title compound was synthesized following Procedure B for Synthesis of Fluorinated Carboxylic Acids as a white solid in 83 %, mp = 250 – 252 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.71 (s, 1H), 8.03 (d, *J* = 8.2 Hz, 1H), 7.88 (dd, *J* = 8.1, 0.6 Hz, 1H), 7.60 (td, *J* = 8.3, 7.1, 1.3 Hz, 1H), 7.52 (td, *J* = 8.1, 7.1, 1.0 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 161.74 (d, *J* = 3.2 Hz), 152.66 (d, *J* = 279.2 Hz), 136.14 (d, *J* = 8.6 Hz), 128.64, 128.41 (d, *J* = 22.5 Hz), 125.63, 123.70 (d, *J* = 1.4 Hz), 121.46 (d, *J* = 1.8 Hz), 112.95 (d, *J* = 8.9 Hz). ^{19}F NMR (376 MHz, DMSO-d_6): δ = -121.02. FTIR (ATR, cm^{-1}): 2805, 2569, 1663, 1599, 1574, 1537, 1446, 1369, 1289, 1043, 900, 755, 729. HRMS (ESI-MS) m/z calcd for $C_9H_6FO_2S$ $[M + H]^+$ 197.0072 found 197.0071.

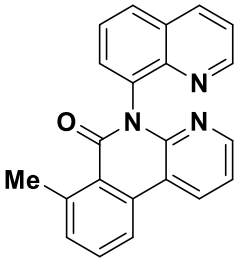


3-fluoro-5-(4-fluorophenyl)thiophene-2-carboxylic acid (4j). The title compound was synthesized following Procedure B for Synthesis of Fluorinated Carboxylic Acids as a white solid in 85% yield, mp = 248 – 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.34 (s, 1H), 7.82 – 7.73 (m, 2H), 7.55 (s, 1H), 7.34 – 7.23 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 162.81 (d, *J* = 247.9 Hz), 160.98 (d, *J* = 3.1 Hz), 158.78 (d, *J* = 273.3 Hz), 145.25 (d, *J* = 9.8 Hz), 128.69 (d, *J* = 3.2 Hz), 127.73 (d, *J* = 8.6 Hz), 116.30 (d, *J* = 22.1 Hz), 115.14 (d, *J* = 25.9 Hz), 112.00 (d, *J* = 9.9 Hz). ^{19}F NMR (376 MHz, DMSO-d_6): δ = -111.40 (tt, *J* = 8.7, 5.2 Hz), -112.89. FTIR (ATR, cm^{-1}): 3096, 2550, 1650, 1598, 1560, 1459, 1442, 1295, 1227, 1161, 1041, 933, 823, 809, 762, 716. HRMS (ESI-MS) m/z calcd for $C_{11}H_7F_2O_2S$ $[M + H]^+$ 241.0134 found 241.0143.



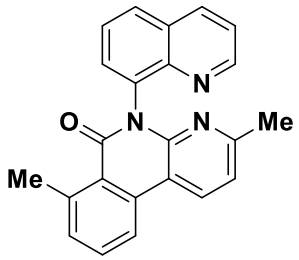
2-fluoro-5-methylpyridine-3-carboxylic acid (4f). The title compound was synthesized following Procedure C for Synthesis of Fluorinated Carboxylic Acids as a white solid in 79% yield, mp = 178 – 180 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.47 (s, 1H), 8.19 – 8.08 (m, 2H), 2.28 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 164.22 (d, *J* = 7.6 Hz), 159.49 (d, *J* = 243.5 Hz), 150.88 (d, *J* = 15.2 Hz), 143.51 (d, *J* = 1.6 Hz), 131.67 (d, *J* = 5.1 Hz), 113.42 (d, *J* = 25.7 Hz), 16.70. ^{19}F NMR (376 MHz, DMSO-d_6): δ = -69.68 (d, *J* = 9.0 Hz). FTIR (ATR, cm^{-1}): 2852, 2610, 1681, 1605, 1463, 1312, 1209, 1113, 906, 789, 748. HRMS (ESI-MS) m/z calcd for $C_7H_7FNO_2$ $[M + H]^+$ 156.0460 found 156.0458.

Characterization of Oxidative Decarboxylative Annulation Products (5)

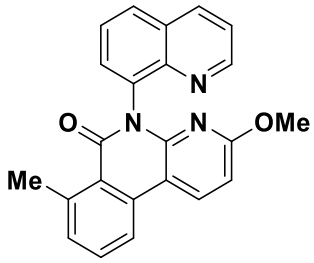


7-methyl-5-(quinolin-8-yl)-5H,6H-benzo[c]1,8-naphthyridin-6-one (5a). The title compound was synthesized following the General Procedure A as an off-white solid in 80% yield (53.9 mg, 0.16 mmol), mp = 271 – 273 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.75 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.54 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.27 – 8.17 (m, 3H), 7.98 (dt, *J* = 7.6, 3.8 Hz, 1H), 7.79 – 7.73 (m, 2H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.38 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.12 (dd, *J* = 7.9, 4.7 Hz, 1H), 2.92 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.71, 150.89, 150.36, 148.85, 144.82, 143.58, 136.59, 136.49, 134.45, 132.58, 132.14, 131.66, 130.39, 129.69, 128.87, 126.72, 124.70, 121.67, 120.29, 118.21, 114.86, 24.50. FTIR (ATR, cm^{-1}): 3030, 2972, 1660, 1584, 1499,

1473, 1394, 1288, 825, 773. HRMS (ESI-MS) m/z calcd for $C_{22}H_{16}N_3O$ $[M + H]^+$ 338.1293 found 338.1291.

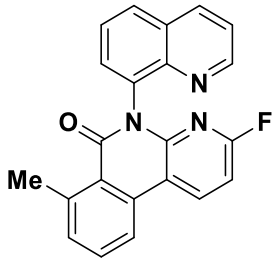


3,7-dimethyl-5-(quinolin-8-yl)-5H,6H-benzo[c]1,8-naphthyridin-6-one (5b). The title compound was synthesized following the General Procedure A and a light brown solid in 67% yield (47.0 mg, 0.13 mmol), mp = 256 – 258 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.75 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.39 (d, *J* = 8.0 Hz, 1H), 8.23 (dd, *J* = 8.4, 1.7 Hz, 1H), 8.15 (d, *J* = 8 Hz, 1H), 7.98 – 7.92 (m, 1H), 7.76 – 7.69 (m, 2H), 7.67 – 7.61 (m, 1H), 7.41 – 7.34 (m, 2H), 6.97 (d, *J* = 8.2 Hz, 1H), 2.91 (s, 3H), 2.19 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.90, 158.34, 150.71, 149.67, 145.07, 143.51, 136.85, 136.34, 134.79, 132.01, 131.93, 131.73, 130.56, 129.53, 128.42, 126.54, 124.43, 121.45, 119.99, 118.06, 111.94, 24.58, 24.54. FTIR (ATR, cm^{-1}): 3049, 2921, 1651, 1592, 1497, 1460, 1383, 1297, 821, 786. HRMS (ESI-MS) m/z calcd for $C_{23}H_{18}N_3O$ $[M + H]^+$ 352.1449 found 352.1450.

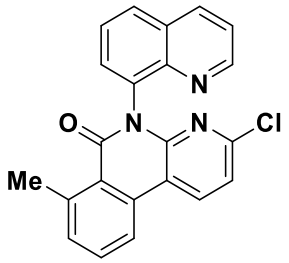


3-methoxy-7-methyl-5-(quinolin-8-yl)-5H,6H-benzo[c]1,8-naphthyridin-6-one (5c). The title compound was synthesized following the General Procedure A as an ochre solid in 36% yield (26.4 mg, 0.07 mmol), mp = 204 – 206 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.77 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.40 (d, *J* = 8.6 Hz, 1H), 8.23 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.06 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.94 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.78 – 7.67 (m, 2H), 7.66 –

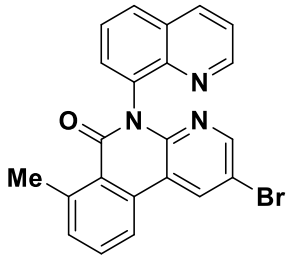
7.59 (m, 1H), 7.38 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.33 (dd, *J* = 7.4, 1.9 Hz, 1H), 6.57 (d, *J* = 8.6 Hz, 1H), 3.12 (s, 3H), 2.92 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ = 163.98, 163.01, 150.79, 148.48, 145.00, 143.57, 136.66, 136.23, 135.21, 134.62, 132.12, 130.97, 130.37, 129.38, 128.45, 126.46, 123.61, 121.46, 119.54, 107.74, 105.60, 53.00, 24.56. FTIR (ATR, cm^{-1}): 3048, 2923, 1651, 1592, 1498, 1461, 1346, 1295, 1257, 1111, 824, 784. HRMS (ESI-MS) m/z calcd for $C_{23}H_{18}N_3O_2$ $[M + H]^+$ 368.1399 found 368.1397.



3-fluoro-7-methyl-5-(quinolin-8-yl)-5H,6H-benzo[c]1,8-naphthyridin-6-one (5d). The title compound was synthesized following the General Procedure A as a white solid in 29% yield (20.6 mg, 0.05 mmol), mp = 336 – 338 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.63 (t, 1H), 8.25 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 8.02 – 7.96 (m, 1H), 7.77 – 7.66 (m, 3H), 7.45 – 7.37 (m, 2H), 6.76 (dd, *J* = 8.5, 3.1 Hz, 1H), 2.90 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ = 163.71, 162.14 (d, *J* = 241.9 Hz), 150.97, 149.00, 144.70, 143.87, 136.94 (d, *J* = 8.8 Hz), 136.49, 135.67, 134.03, 132.40 (d, *J* = 10.4 Hz), 130.39, 129.72, 129.14, 126.67, 124.24, 121.75, 120.10, 112.37 (d, *J* = 4.6 Hz), 103.69, 103.31, 24.49. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -65.85 (dd, *J* = 7.6, 3.0 Hz). FTIR (ATR, cm^{-1}): 3050, 2923, 1652, 1588, 1498, 1454, 1292, 1224, 823, 798, 786. HRMS (ESI-MS) m/z calcd for $C_{22}H_{15}FN_3O$ $[M + H]^+$ 356.1199 found 356.1198.

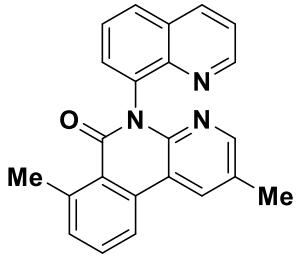


3-chloro-7-methyl-5-(quinolin-8-yl)-5H,6H-benzo[c]1,8-naphthyridin-6-one (5e). The title compound was synthesized following the General Procedure A as a white solid in 27% (20.0 mg, 0.05 mmol), mp = 326 – 328 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.47 (d, *J* = 8.2 Hz, 1H), 8.25 (dd, *J* = 8.4, 1.7 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 8.01 – 7.96 (m, 1H), 7.77 – 7.71 (m, 2H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.14 (d, *J* = 8.2 Hz, 1H), 2.90 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.53, 150.90, 149.93, 144.72, 143.88, 136.47, 135.79, 134.10, 133.83, 132.81, 132.40, 130.48, 129.65, 129.00, 126.63, 124.59, 121.68, 120.32, 118.48, 113.48, 24.48. FTIR (ATR, cm^{-1}): 3093, 2924, 1661, 1599, 1579, 1498, 1439, 1391, 1286, 1128, 1076, 867, 816, 788. HRMS (ESI-MS) m/z calcd for $C_{22}H_{15}ClN_3O$ $[M + H]^+$ 372.0903 found 372.0900.

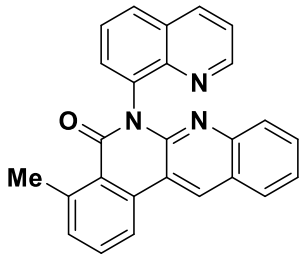


2-bromo-7-methyl-5-(quinolin-8-yl)-5H,6H-benzo[c]1,8-naphthyridin-6-one (5s). The title compound was synthesized following the General Procedure A. White solid in 40% (33.3 mg, 0.08 mmol), mp = 294 – 296 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.65 (d, *J* = 2.2 Hz, 1H), 8.25 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.21 (d, *J* = 2.2 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.99 (dt, *J* = 7.4, 3.7 Hz, 1H), 7.78 – 7.67 (m, 3H), 7.47 (d, *J* = 7.4 Hz, 1H), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.90 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.41, 151.03, 149.35, 148.99, 144.70, 143.91, 136.52, 136.11, 133.85, 133.35, 133.27, 132.40, 130.31, 129.71, 129.10, 126.71, 124.87, 121.80, 120.48,

116.48, 113.69, 24.45. FTIR (ATR, cm^{-1}): 3048, 2928, 1665, 1597, 1499, 1465, 1388, 1288, 964, 827, 795, 689. HRMS (ESI-MS) m/z calcd for $C_{22}H_{15}BrN_3O$ $[M + H]^+$ 416.0398 found 416.0396.

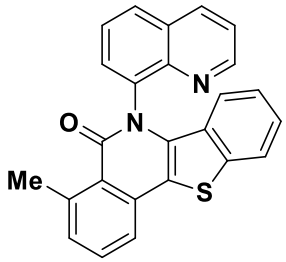


2,7-dimethyl-5-(quinolin-8-yl)-5H,6H-benzo[c]1,8-naphthyridin-6-one (5f). The title compound was synthesized following the General Procedure A as a light brown solid in 70% yield (49.2 mg, 0.14 mmol), mp = 276 – 278 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.76 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.37 – 8.32 (m, 1H), 8.24 (dd, *J* = 8.3, 1.5 Hz, 1H), 8.19 (d, *J* = 8.1 Hz, 1H), 8.07 – 8.02 (m, 1H), 7.98 (dd, *J* = 6.8, 2.8 Hz, 1H), 7.79 – 7.72 (m, 2H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.44 – 7.35 (m, 2H), 2.92 (s, 3H), 2.36 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.63, 150.87, 149.29, 148.54, 144.88, 143.51, 136.69, 136.46, 134.39, 132.43, 131.99, 131.93, 130.40, 129.68, 128.81, 127.36, 126.70, 124.74, 121.62, 120.24, 114.28, 24.52, 18.06. FTIR (ATR, cm^{-1}): 3050, 2920, 1652, 1599, 1479, 1301, 805, 782. HRMS (ESI-MS) m/z calcd for $C_{23}H_{18}N_3O$ $[M + H]^+$ 352.1449 found 352.1450.

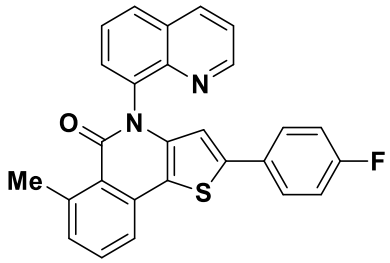


8-methyl-6-(quinolin-8-yl)-6,7-dihydro-5,6-diazatetraphen-7-one (5h). The title compound was synthesized following the General Procedure A as a white solid in 51% yield (39.5 mg, 0.10 mmol), mp = 332 – 334 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.99

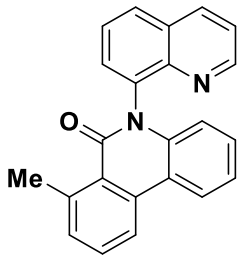
(s, 1H), 8.71 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.38 (d, *J* = 8.0 Hz, 1H), 8.26 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.01 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.88 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.83 – 7.74 (m, 2H), 7.70 (t, *J* = 7.8 Hz, 1H), 7.53 – 7.43 (m, 3H), 7.41 – 7.34 (m, 2H), 2.92 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ = 164.11, 150.80, 149.81, 147.20, 145.02, 143.81, 136.86, 136.41, 134.33, 133.01, 132.27, 131.62, 130.69, 130.18, 129.67, 128.59, 128.37, 127.91, 126.68, 125.29, 124.95, 124.67, 121.55, 120.66, 115.99, 24.54. FTIR (ATR, cm^{-1}): 3049, 2923, 1652, 1599, 1499, 1280, 881, 803. HRMS (ESI-MS) m/z calcd for $C_{26}H_{18}N_3O$ $[M + H]^+$ 388.1449 found 388.1450.



8-methyl-6-(quinolin-8-yl)-6H,7H-benzothieno[3,2-c]isoquinolin-7-one (5i). The title compound was synthesized following the General Procedure C as a yellow solid in 44% yield (34.5 mg, 0.08 mmol), mp = 240 – 242 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.78 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.30 (dd, *J* = 8.4, 1.7 Hz, 1H), 8.12 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.88 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.82 – 7.73 (m, 2H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.62 (t, *J* = 7.7 Hz, 1H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.34 (d, *J* = 7.3 Hz, 1H), 7.15 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H), 6.73 (ddd, *J* = 8.4, 7.1, 1.1 Hz, 1H), 5.68 (dd, *J* = 8.0, 1.0 Hz, 1H, 2.94 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ = 163.73, 151.61, 145.05, 143.58, 138.36, 137.37, 136.31, 134.87, 133.71, 132.34, 130.86, 130.46, 129.68, 129.45, 126.65, 125.25, 124.04, 123.15, 123.01, 122.48, 122.10, 121.75, 117.75, 24.12. FTIR (ATR, cm^{-1}): 3067, 2922, 1645, 1597, 1497, 1388, 1294, 905, 814, 727. HRMS (ESI-MS) m/z calcd for $C_{25}H_{17}N_2OS$ $[M + H]^+$ 393.1061 found 393.1061.

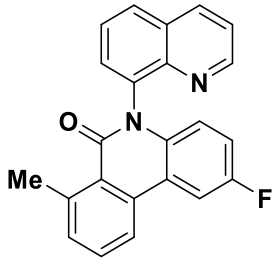


2-(4-fluorophenyl)-6-methyl-4-(quinolin-8-yl)-4H,5H-thieno[3,2-c]isoquinolin-5-one (5j). The title compound was synthesized following the General Procedure B as a yellow solid in 23% yield (20.1 mg, 0.04 mmol), mp = 250 – 252 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.87 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.28 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.03 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.84 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.75 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.62 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.26 (dt, *J* = 7.3, 1.1 Hz, 1H), 7.02 – 6.93 (m, 2H), 6.22 (s, 1H), 2.90 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.05, 162.65 (d, *J* = 248.0 Hz), 151.49, 144.31, 143.75, 142.20, 141.40, 137.04, 136.31, 134.69, 132.24, 130.13, 130.03, 129.87 (d, *J* = 3.4 Hz), 129.74, 129.41, 127.51 (d, *J* = 8.1 Hz), 126.66, 122.44, 122.01, 120.57, 116.72, 115.83 (d, *J* = 22.0 Hz), 114.18, 24.20. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -112.96 – -113.13 (m). FTIR (ATR, cm^{-1}): 3067, 2920, 1640, 1598, 1492, 1228, 882, 818, 787. HRMS (ESI-MS) m/z calcd for $C_{27}H_{18}FN_2OS$ $[M + H]^+$ 437.1123 found 437.1124.

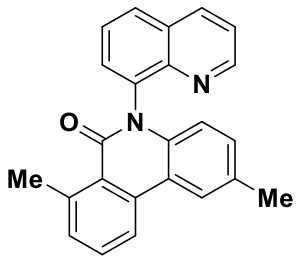


7-methyl-5-(quinolin-8-yl)-5,6-dihydrophenanthridin-6-one (5j). The title compound was synthesized following the General Procedure B as an off white solid in 68% (45.8 mg, 0.13 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.81 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.36 – 8.24 (m, 3H), 8.02 (dd, *J* = 7.3, 2.4 Hz, 1H), 7.82 – 7.73 (m, 2H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.41 (dt, *J* = 8.6, 4.4 Hz, 2H), 7.18 (dtd, *J* = 19.0, 7.3, 1.4 Hz, 2H), 6.41 (dd, *J* = 8.1, 1.5 Hz, 1H), 2.95 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 162.87, 151.40, 144.73,

143.18, 139.70, 136.70, 136.41, 136.05, 131.94, 131.80, 130.76, 129.93, 129.25, 128.96, 126.94, 124.51, 123.49, 122.20, 121.98, 120.25, 119.32, 116.51, 24.64. The spectral data are consistent with those reported in the literature.[65]

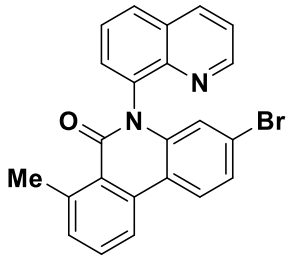


2-fluoro-7-methyl-5-(quinolin-8-yl)-5,6-dihydrophenanthridin-6-one (5k). The title compound was synthesized following the General Procedure B as an ochre solid in 62% yield (43.8 mg, 0.12 mmol), mp = 237 – 239 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.81 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.28 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.15 (d, *J* = 8.2 Hz, 1H), 8.06 – 8.00 (m, 1H), 7.96 (dd, *J* = 10.2, 2.8 Hz, 1H), 7.79 – 7.73 (m, 2H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.3 Hz, 2H), 6.87 (ddd, *J* = 9.3, 7.6, 2.8 Hz, 1H), 6.34 (dd, *J* = 9.2, 4.9 Hz, 1H), 2.92 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 162.57, 158.48 (d, *J* = 240.3 Hz), 151.54, 144.70, 143.48, 136.62, 136.51, 136.21 (d, *J* = 1.8 Hz), 135.19 (d, *J* = 2.8 Hz), 132.52, 132.10, 130.83, 130.04, 129.46, 127.03, 124.75, 122.12, 120.61 (d, *J* = 7.7 Hz), 120.51, 118.03 (d, *J* = 8.2 Hz), 116.42 (d, *J* = 23.6 Hz), 109.39 (d, *J* = 24.1 Hz), 24.60. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -121.35 (ddd, *J* = 10.2, 7.5, 4.8 Hz). FTIR (ATR, cm^{-1}): 3073, 2924, 1652, 1592, 1481, 1396, 1303, 1205, 961, 828, 799, 758. HRMS (ESI-MS) m/z calcd for $C_{23}H_{16}FN_2O$ $[M + H]^+$ 355.1246 found 355.1245.

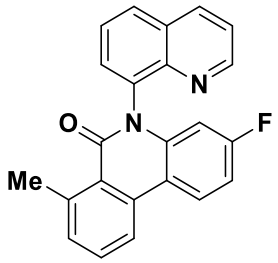


2,7-dimethyl-5-(quinolin-8-yl)-5,6-dihydrophenanthridin-6-one (5l). The title compound was synthesized following the General Procedure B as a light brown solid in

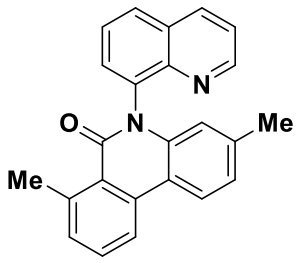
56% yield (39.2 mg, 0.11 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.81 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.32 – 8.24 (m, 2H), 8.12 (s, 1H), 8.01 (dd, *J* = 6.4, 3.3 Hz, 1H), 7.79 – 7.72 (m, 2H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.45 – 7.36 (m, 2H), 6.97 (dd, *J* = 8.5, 1.7 Hz, 1H), 6.28 (d, *J* = 8.5 Hz, 1H), 2.93 (s, 3H), 2.42 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 162.82, 151.44, 144.81, 143.25, 137.72, 136.89, 136.44, 136.05, 131.86, 131.73, 131.51, 130.81, 130.09, 129.97, 129.21, 126.98, 124.64, 123.61, 121.98, 120.24, 119.16, 116.44, 24.70, 21.17. The spectral data are consistent with those reported in the literature.[65]



3-bromo-7-methyl-5-(quinolin-8-yl)-5,6-dihydrophenanthridin-6-one (5m). The title compound was synthesized following the General Procedure B as an off white solid in 36% yield (29.7 mg, 0.07 mmol), mp = 253 – 255 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.81 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.29 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.20 (d, *J* = 8.2 Hz, 1H), 8.15 (d, *J* = 8.7 Hz, 1H), 8.04 (dd, *J* = 7.3, 2.4 Hz, 1H), 7.80 – 7.72 (m, 2H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.40 (d, *J* = 7.4 Hz, 1H), 7.31 (dd, *J* = 8.7, 1.9 Hz, 1H), 6.53 (d, *J* = 1.9 Hz, 1H), 2.89 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 162.73, 151.63, 144.57, 143.49, 140.77, 136.59, 136.09, 135.45, 132.25, 132.24, 130.77, 130.09, 129.72, 127.04, 125.40, 125.02, 124.42, 123.03, 122.23, 120.22, 119.11, 118.43, 24.60. FTIR (ATR, cm^{-1}): 3060, 2921, 1651, 1594, 1499, 1464, 1387, 1301, 802, 783, 685. HRMS (ESI-MS) m/z calcd for $C_{23}H_{16}BrN_2O$ $[M + H]^+$ 415.0445 found 415.0447.

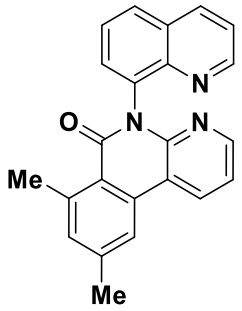


3-fluoro-7-methyl-5-(quinolin-8-yl)-5,6-dihydrophenanthridin-6-one (5n). The title compound was synthesized following the General Procedure B as an off white solid in 68% (48.7 mg, 0.13 mmol), mp = 233 – 235 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.81 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.32 – 8.23 (m, 2H), 8.16 (d, *J* = 8.2 Hz, 1H), 8.08 – 8.00 (m, 1H), 7.79 – 7.74 (m, 2H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.37 (d, *J* = 7.4 Hz, 1H), 6.91 (ddd, *J* = 9.0, 7.9, 2.6 Hz, 1H), 6.08 (dd, *J* = 10.8, 2.6 Hz, 1H), 2.91 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.04 (d, *J* = 246.9 Hz), 162.99, 151.56, 144.49, 143.38, 141.22 (d, *J* = 10.7 Hz), 136.55, 136.28, 135.65, 132.21, 131.64, 130.69, 130.06, 129.63, 127.00, 125.48 (d, *J* = 9.8 Hz), 123.89 (d, *J* = 1.2 Hz), 122.17, 120.12, 115.85 (d, *J* = 2.5 Hz), 109.89 (d, *J* = 22.6 Hz), 103.29 (d, *J* = 26.9 Hz), 24.60. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -111.14 – -111.28 (m). FTIR (ATR, cm^{-1}): 3067, 2967, 1654, 1598, 1459, 1388, 1301, 1144, 823, 784. HRMS (ESI-MS) m/z calcd for $C_{23}H_{16}FN_2O$ $[M + H]^+$ 355.1246 found 355.1246.

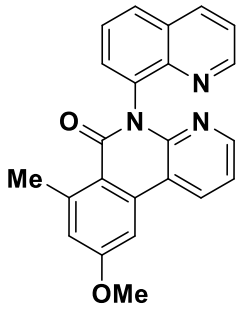


3,7-dimethyl-5-(quinolin-8-yl)-5,6-dihydrophenanthridin-6-one (5o). The title compound was synthesized following the General Procedure B as a light brown solid in

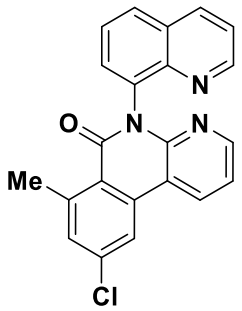
50% yield (35.1 mg, 0.10 mmol), mp = 218 – 220 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.82 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.28 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.24 (d, *J* = 8.2 Hz, 1H), 8.19 (d, *J* = 8.3 Hz, 1H), 8.07 – 7.98 (m, 1H), 7.82 – 7.73 (m, 2H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.02 (d, *J* = 8 Hz, 1H), 6.18 (s, 1H), 2.91 (s, 3H), 2.15 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.08, 151.50, 144.87, 143.21, 139.75, 139.34, 136.89, 136.49, 136.27, 131.94, 131.36, 130.82, 129.98, 129.26, 127.00, 124.18, 123.61, 123.47, 122.03, 120.05, 117.02, 116.64, 24.67, 21.70. FTIR (ATR, cm^{-1}): 3067, 2920, 1646, 1598, 1498, 1462, 1390, 1300, 822, 788. HRMS (ESI-MS) m/z calcd for $C_{24}H_{19}N_2O$ $[M + H]^+$ 351.1497 found 351.1498.



7,9-dimethyl-5-(quinolin-8-yl)-5H,6H-benzo[c]1,8-naphthyridin-6-one (5q): The title compound was synthesized following the General Procedure A as a merlot solid in 75% yield (53.2 mg, 0.15 mmol), mp = 294 – 296 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.75 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.52 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.23 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.19 (dd, *J* = 4.6, 1.7 Hz, 1H), 8.00 – 7.94 (m, 2H), 7.79 – 7.70 (m, 2H), 7.37 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.25 (s, 1H), 7.09 (dd, *J* = 8.0, 4.7 Hz, 1H), 2.88 (s, 3H), 2.52 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.70, 150.88, 150.50, 148.69, 144.90, 143.36, 142.54, 136.70, 136.45, 134.48, 133.90, 131.59, 130.42, 129.67, 128.81, 126.70, 122.38, 121.64, 120.47, 118.09, 114.83, 24.31, 21.94. FTIR (ATR, cm^{-1}): 3050, 2922, 1645, 1598, 1499, 1464, 1392, 1300, 823, 789. HRMS (ESI-MS) m/z calcd for $C_{23}H_{18}N_3O$ $[M + H]^+$ 352.1449 found 352.1447.

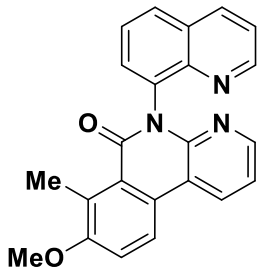


9-methoxy-7-methyl-5-(quinolin-8-yl)-5H,6H-benzo[c]1,8-naphthyridin-6-one (5r). The title compound was synthesized following the General Procedure A as a merlot solid in 71% yield (52.2 mg, 0.14 mmol), mp = 303 – 305 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.75 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.48 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.27 – 8.19 (m, 2H), 7.97 (dt, *J* = 7.4, 3.7 Hz, 1H), 7.77 – 7.71 (m, 2H), 7.59 (d, *J* = 2.5 Hz, 1H), 7.38 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.11 (dd, *J* = 8.0, 4.7 Hz, 1H), 6.99 (d, *J* = 1.9 Hz, 1H), 3.99 (s, 3H), 2.88 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.41, 162.11, 150.92, 150.67, 149.06, 146.13, 144.97, 136.71, 136.57, 136.49, 131.71, 130.50, 129.70, 128.82, 126.73, 121.65, 119.56, 118.57, 118.00, 114.71, 103.70, 55.61, 24.80. FTIR (ATR, cm^{-1}): 3004, 2921, 1652, 1601, 1500, 1452, 1399, 1306, 1291, 1166, 1049, 814, 784. HRMS (ESI-MS) m/z calcd for $C_{23}H_{18}N_3O_2$ $[M + H]^+$ 368.1399 found 368.1396.

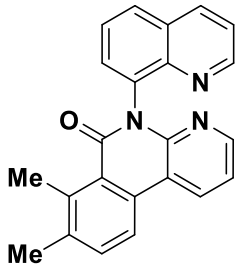


9-chloro-7-methyl-5-(quinolin-8-yl)-5H,6H-benzo[c]1,8-naphthyridin-6-one (5s). The title compound was synthesized following the General Procedure A as a terra cotta solid in 63% yield (46.6 mg, 0.12 mmol), mp = 284 – 286 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.75 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.45 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.27 – 8.20 (m, 2H), 8.15 (d, J= 2.0 Hz,1H), 7.99 (dd, *J* = 6.4, 3.3 Hz, 1H), 7.78 – 7.71 (m, 2H), 7.43 – 7.35 (m, 2H), 7.11 (dd, *J* = 8.0, 4.7 Hz, 1H), 2.89 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ =

163.04, 150.93, 150.47, 149.54, 145.81, 144.69, 138.59, 136.50, 136.25, 135.98, 132.30, 131.85, 130.34, 129.67, 128.99, 126.68, 123.12, 121.73, 120.14, 118.38, 113.81, 24.35. FTIR (ATR, cm^{-1}): 3067, 2923, 1661, 1592, 1501, 1470, 1396, 1300, 825, 783, 760. HRMS (ESI-MS) m/z calcd for $C_{22}H_{15}ClN_3O$ $[M + H]^+$ 372.0903 found 372.0903.

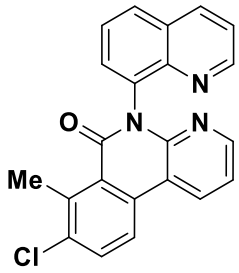


8-methoxy-7-methyl-5-(quinolin-8-yl)-5H,6H-benzo[c]1,8-naphthyridin-6-one (5t). The title compound was synthesized following the General Procedure A as an off white solid in 54% yield (40.0 mg, 0.10 mmol), mp = 337 – 339 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.74 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.48 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.24 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.20 (d, *J* = 8.9 Hz, 1H), 8.16 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.00 – 7.95 (m, 1H), 7.77 – 7.71 (m, 2H), 7.43 – 7.35 (m, 2H), 7.12 (dd, *J* = 7.9, 4.7 Hz, 1H), 3.97 (s, 3H), 2.82 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 163.85, 158.47, 150.96, 149.80, 147.78, 144.92, 136.87, 136.49, 131.47, 130.72, 130.42, 129.71, 128.84, 127.17, 126.74, 125.75, 121.67, 120.82, 118.22, 115.93, 115.13, 56.49, 13.90. FTIR (ATR, cm^{-1}): 3012, 2936, 1655, 1594, 1495, 1452, 1030, 1274, 1163, 1069, 827, 789. HRMS (ESI-MS) m/z calcd for $C_{23}H_{18}N_3O_2$ $[M + H]^+$ 368.1399 found 368.1397.

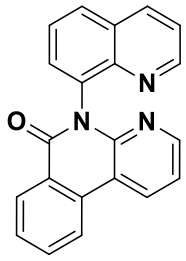


7,8-dimethyl-5-(quinolin-8-yl)-5H,6H-benzo[c]1,8-naphthyridin-6-one (5u). The title compound was synthesized following the General Procedure A as an off white solid in

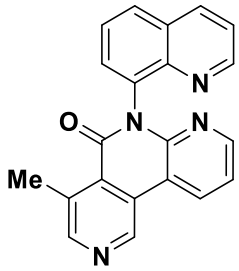
70% yield (49.0 mg, 0.13 mmol), mp = 329 – 331 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.52 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.24 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.19 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 8.02 – 7.95 (m, 1H), 7.78 – 7.72 (m, 2H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.38 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.12 (dd, *J* = 7.9, 4.7 Hz, 1H), 2.86 (s, 3H), 2.48 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 164.05, 150.89, 150.15, 148.42, 141.75, 138.88, 136.87, 136.55, 136.53, 134.56, 132.47, 131.25, 130.43, 129.70, 128.82, 126.75, 124.71, 121.66, 119.47, 118.16, 115.03, 21.58, 18.53. FTIR (ATR, cm^{-1}): 3010, 2970, 1651, 1587, 1497, 1385, 1299, 829, 791. HRMS (ESI-MS) m/z calcd for $C_{23}H_{18}N_3O$ $[M + H]^+$ 352.1449 found 352.1447.



8-chloro-7-methyl-5-(quinolin-8-yl)-5H,6H-benzo[c]1,8-naphthyridin-6-one (5v). The title compound was synthesized following the General Procedure A as a dark brown solid in 31% yield (22.9 mg, 0.06 mmol), mp = 344 – 346 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.52 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.29 – 8.21 (m, 2H), 8.15 (d, *J* = 8.7 Hz, 1H), 7.99 (dt, *J* = 7.3, 3.7 Hz, 1H), 7.82 (d, *J* = 8.7 Hz, 1H), 7.78 – 7.72 (m, 2H), 7.39 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.17 (dd, *J* = 8.0, 4.6 Hz, 1H), 3.01 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.04, 151.02, 150.26, 149.27, 144.72, 140.95, 136.88, 136.54, 136.47, 133.59, 133.28, 131.63, 130.30, 129.73, 129.04, 126.73, 126.24, 121.78, 120.87, 118.45, 114.25, 19.34. FTIR (ATR, cm^{-1}): 3050, 2999, 1652, 1587, 1499, 1451, 1369, 1300, 811, 786, 707. HRMS (ESI-MS) m/z calcd for $C_{22}H_{15}ClN_3O$ $[M + H]^+$ 372.0903 found 372.0900.



5-(quinolin-8-yl)-5H,6H-benzo[c]1,8-naphthyridin-6-one (5w). The title compound was synthesized following the General Procedure A as a light red solid in 48% yield (31.3 mg, 0.09 mmol), mp = 262 – 264 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.61 – 8.56 (m, 2H), 8.32 (dd, *J* = 8.3, 1.3 Hz, 1H), 8.29 – 8.23 (m, 2H), 8.00 (dd, *J* = 7.1, 2.5 Hz, 1H), 7.87 – 7.81 (m, 1H), 7.80 – 7.72 (m, 2H), 7.69 – 7.63 (m, 1H), 7.38 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.19 (dd, *J* = 7.8, 4.6 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ = 162.94, 150.99, 150.39, 148.94, 144.77, 136.47, 136.16, 133.16, 132.99, 131.41, 130.36, 129.64, 129.51, 129.08, 128.85, 126.64, 126.37, 122.08, 121.70, 118.52, 114.88. FTIR (ATR, cm^{-1}): 3032, 2999, 1652, 1587, 1499, 1451, 1369, 1300, 811, 785. HRMS (ESI-MS) m/z calcd for $C_{21}H_{14}N_3O$ $[M + H]^+$ 324.1136 found 324.1133.



4-methyl-6-(quinolin-8-yl)-5H,6H-pyrido[4,3-c]1,8-naphthyridin-5-one (5x). The title compound was synthesized following the General Procedure A as a terra cotta solid in 61% yield (41.4 mg, 0.12 mmol), mp = 335 – 337 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.61 (s, 1H), 8.73 (dd, *J* = 4.3, 1.6 Hz, 1H), 8.71 – 8.65 (m, 2H), 8.31 – 8.23 (m, 2H), 8.04 – 7.97 (m, 1H), 7.80 – 7.72 (m, 2H), 7.41 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.22 (dd, *J* = 7.8, 4.6 Hz, 1H), 2.87 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ = 162.62, 151.78, 151.08,

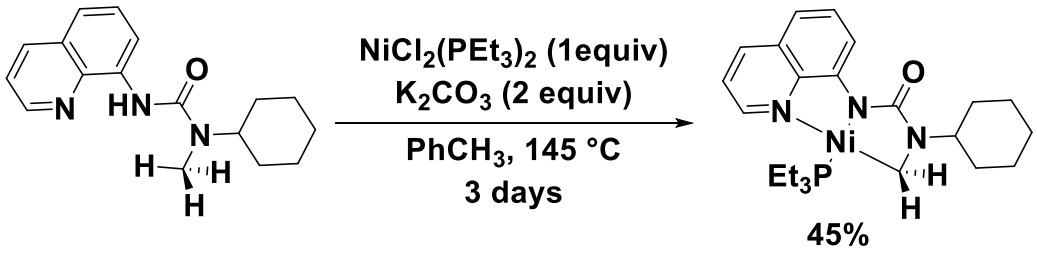
150.61, 149.83, 144.54, 143.97, 136.55, 135.83, 135.33, 131.30, 130.20, 129.72, 129.67, 129.26, 127.83, 126.70, 121.88, 118.84, 112.92, 20.25. FTIR (ATR, cm^{-1}): 3048, 2956, 1659, 1593, 1448, 1407, 1298, 827, 786. HRMS (ESI-MS) m/z calcd for $C_{21}H_{15}N_4O$ $[M + H]^+$ 339.1245 found 339.1243.

Chapter 4: Synthetic Routes to a Possible Nickel(II) Metallacycle: Denitrogenation and Decarbonylation

4.1. Overview

Nickel complexes have been widely employed as catalyst in C–C and C-heteroatom bond transformations in traditional cross-coupling reactions.[1] While nickel has experienced a revival as an economical and complementary alternative to palladium-catalyzed methods in recent years, the mechanism of nickel-catalyzed reactions are not fully understood. However, many of these reactions involve a proposed Ni(II) metallacycle complex to result from C–H activation[41,72] allowing the proposed Ni(II) metallacycle to react with a coupling partner through either a two electron or single electron pathway.[73] Despite the ubiquity of these proposed species in catalytic cycles, such a complex has not yet been isolated or shown to be catalytically relevant.

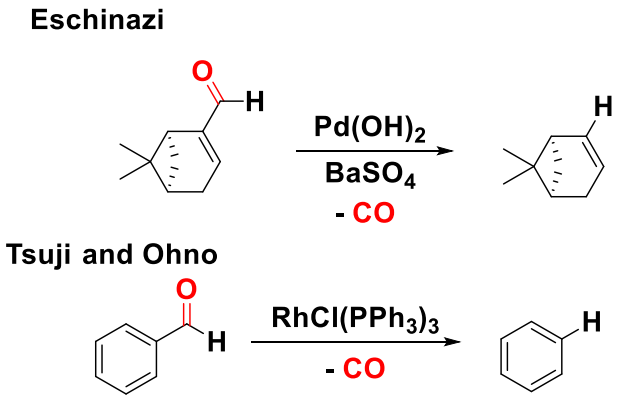
In the revival of nickel catalysis, many groups have begun to isolate and study elusive Ni(III) and Ni(IV) dialkyl/aryl complexes. Mirica and Sanford demonstrated that a cleverly designed tetradentate or tridentate nitrogen donor ligand could be used to stabilize an isolable Ni(III) or Ni(IV) dialkyl/aryl complex.[74] More recently, the Love group has reported a Ni(II) metallacycle from sp^3 C–H activation of a urea moiety (Scheme 23).[75] The urea moiety was needed in order to stabilize the Ni(II) metallacycle. In addition, the Love group also showed the metallacycle would react with a small set of coupling partners, but in low yields (20 – 48%). Unfortunately, this urea moiety has not been shown to be catalytically relevant.



Scheme 23. Ni(II)-mediated sp^3 C–H activation of a tertiary urea moiety.

We have recently proposed a Ni(II) metallacycle in our oxidative decarboxylative (hetero)arylation and annulation reactions above in chapters 2 and 3.[66,76] Under our reaction conditions, we proposed the Ni(II) metallacycle intermediate to undergo transmetallation with a silver(I)-aryl and concomitant oxidation to form the desired product. However, in order to study our proposed reaction, we first had to isolate the Ni(II) intermediate. We then hypothesized the desired metallacycle could be isolated through either denitrogenation or decarbonylation.

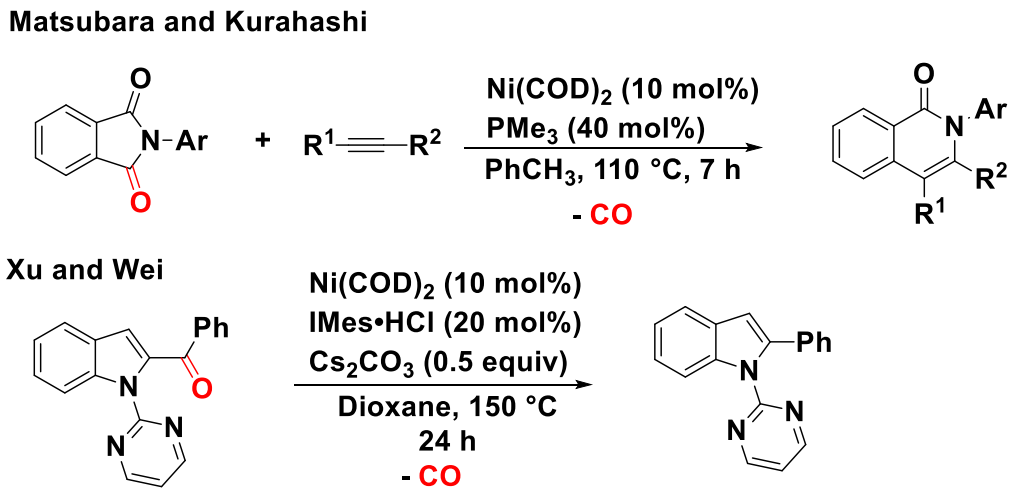
Similar to decarboxylative coupling reactions discussed above, decarbonylation reactions represent another approach in creating a metal–C bond. This involves the insertion of a transition-metal into an aroyl compound and extruding carbon monoxide. One of the first reported transition-metal mediated decarbonylations was reported from Eschinazi.[77] Eschinazi found that aldehydes undergo decarbonylation in the presence of palladium. Later, Tsuji and Ohno reported the decarbonylation of primary or aryl aldehydes and acyl halides by stoichiometric amounts of Wilkinson's catalyst ($RhCl(PPh_3)_3$) (Scheme 24).[78] Since then, decarbonylation has been utilized in other functional groups including carboxylic acids[79], esters[80], anhydrides[81], phthalimides[82], and unstrained ketones.[83]



Scheme 24. First reported transition-metal-mediated decarbonylation.

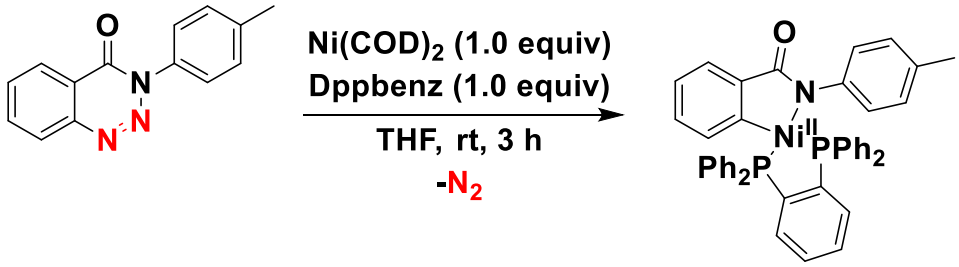
More recently, nickel-catalyzed decarbonylative annulations of phthalimides have been reported. In 2008, Matsubara and Kurahashi postulated that a Ni(0) with electron-rich phosphines would oxidatively add to the C–N bond thereby creating a C–Ni–N species

after decarbonylation and allowing a variety of unsaturated alkynes to undergo insertion.[84] There have also been reports of a directed nickel-catalyzed decarbonylation of unstrained ketones from Xu and Wei.[85] Where they found *N*-pyrimidinyl 2-benzoyl indole as their model substrate would undergo decarbonylation to form a biaryl in the presence of $Ni(COD)_2$ with a NHC and Cs_2CO_3 in dioxane. In addition, the directing group did not shut down the Ni-catalyst due to heterocyclic poisoning (Scheme 25).



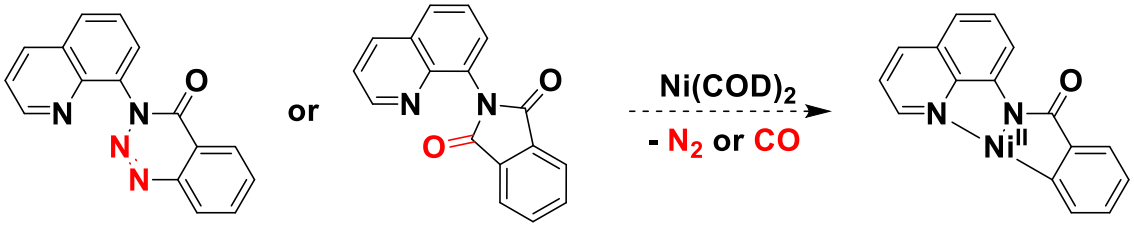
Scheme 25. Ni-catalyzed decarbonylation of unstrained ketones and phthalimides.

On the other hand, transition-metal catalyzed denitrogenative functionalization of triazole rings has attracted attention as an alternative to traditional synthesis for the construction of heterocyclic compounds. Early pioneering work from Gevorgyan[86] and Fokin[87] in Rh-catalyzed transannulation of triazoles with nitriles and alkynes highlighted this utility. Murakami and co-workers were the first to report a nickel-catalyzed denitrogenative annulation of 1,2,3-benzotriazin-4(3*H*)-ones with various unsaturated compounds.[88] They discovered when using $Ni(COD)_2$ in combination with a phosphine ligand, $Ni(COD)_2$ inserted into the N–N bond thereby producing dinitrogen and an azanickelacycle. This was later confirmed by adding stoichiometric amounts of $Ni(COD)_2$ and Dppbenz to *N*-toyl-1,2,3-benzotriazine-4(3*H*)-one to afford an isolable five-membered azanickelacycle (Scheme 26).[89] Other groups have also reported annulation reactions with alkenes,[90] isocyanides,[91] benzynes,[92] and cross-coupling with boronic acids.[93]



Scheme 26. Formation of a five-membered azanickelacycle by denitrogenation.

Since Ni(0) has been shown to insert in to the C–N bond of phthalimide and the N–N of triazole rings we hypothesized we would be able to synthesize the Ni(II) metallacycle from 3-(quinolin-8-yl)-3,4-dihydro-1,2,3-benzotriazin-4-one or 2-(quinolin-8-yl)-2,3-dihydro-1H-isoindole-1,3-dione in the presence of a Ni(0) source (Scheme 27). Access to the targeted metallacycle would allow us to probe our proposed reaction mechanism, discussed earlier in Chapters 2 and 3.



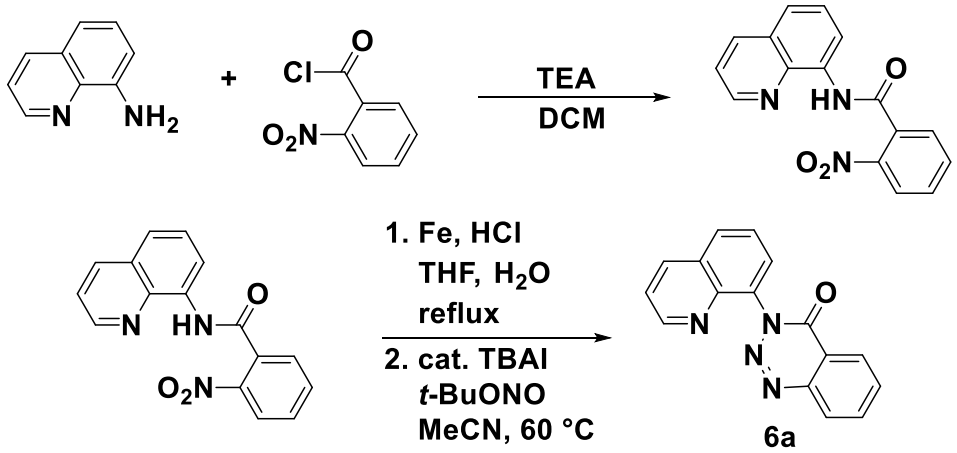
Scheme 27. Proposed synthesis of a Ni(II) metallacycle from phthalimide or 1,2,3-benzotriazine.

4.2. Results

4.2.1. Synthesis of 1,2,3-Benzotriazine Derivative and Attempted Denitrogenation for Ni(II) Metallacycle

Since triazoles have been reported to undergo denitrogenation in the presence of $Ni(COD)_2$, we set out to synthesize a 1,2,3-benzotriazine linked quinoline in hopes of isolating the proposed Ni(II) metallacycle. The 2-nitro-*N*-(quinolin-8-yl)benzamide was synthesized from a modified reported procedure.[94] 2-nitrobenzoyl chloride and 8-aminoquinoline were allowed to stir overnight, providing 67% yield after purification.[95] The corresponding 2-nitro-*N*-(quinolin-8-yl)benzamide was then reduced using a

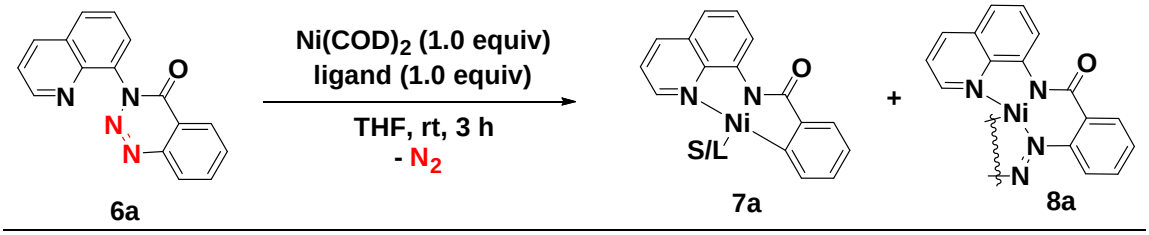
Béchamp reduction to afford the corresponding 2-amino-*N*-(quinolin-8-yl)benzamide. The substituted 2-aminobenazide product then afforded the desired annulation product from a reported procedure (Scheme 28).[96]



Scheme 28. Synthesis of 3-(quinolin-8-yl)-3,4-dihydro-1,2,3-benzotriazin-4-one from 8-aminoquinoline and 2-nitrobenzoyl chloride.

The reaction of 3-(quinolin-8-yl)-3,4-dihydro-1,2,3-benzotriazin-4-one (**6a**) was treated with equimolar amounts of $Ni(COD)_2$ and a ligand in THF at room temperature causing the solution to turn dark brown. After stirring for 3 h, the mixture was concentrated down to minimum amount of THF. The reaction mixture was then precipitated out of solution into pentane dropwise producing a dark brown solid. The solid was then dried under high vacuum for 2 h.

Table 4.1. Attempted synthesis of a Ni(II) metallacycle by denitrogenation[a]



6a 7a 8a

entry	Ligand	Yield **7a** (%)	Yield **8a** (%)
1	PPh_3	0	74
2	MeCN	0	44
3	Dppbenz	0	63
4	none	0	71

[a]Isolated yields. Reaction conditions: **6a** (0.2 mmol), $Ni(COD)_2$ (0.2 mmol), ligand (0.2 mmol) in THF (8 mL).

$Ni(COD)_2$ was treated with **6a** with in order to obtain the Ni(II) metallacycle complex. Characterization of the isolated products (Table 4.1, entry 1-4) showed the same diamagnetic ^1H NMR spectrum when ligands or no ligands were added. The ^1H NMR spectrum of **8a** shows eight inequivalent aryl resonances adding up to ten protons. The $^{13}C\{^1H\}$ NMR spectrum shows fifteen different aryl resonances and one carbonyl resonance. The carbonyl resonance at δ 167.0 is indicative of a typical six-membered azanickel metallacycle.[97] Recrystallization of the reaction mixture from CH_2Cl_2/Hexane afforded complex **8a** as dark brown crystals. The structure of **8a** was established by single-crystal X-ray analysis to contain a square planar Ni(II) dimeric molecule in a bowl-shaped structure $[(C_{16}H_{10}N_4O)Ni]_2$ (Figure 2).

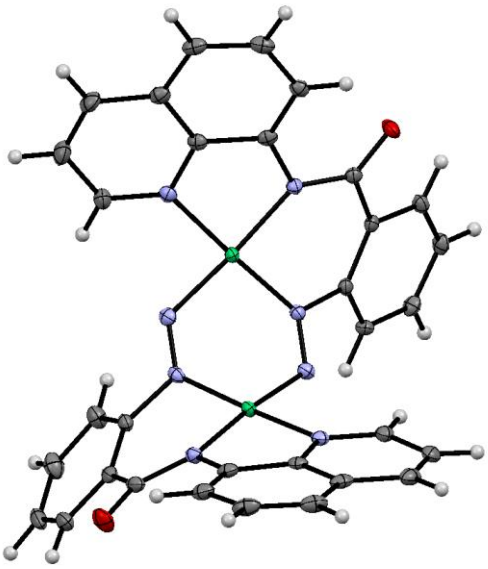
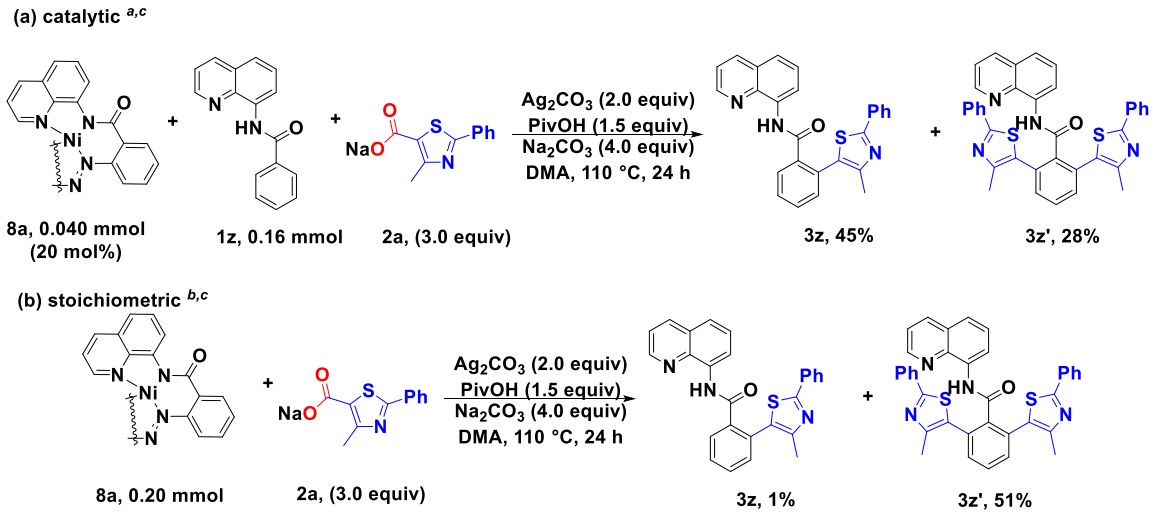


Figure 2. Perspective view of the molecular structure of $[(C_{16}H_{10}N_4O)Ni]_2$ (**8a**) with the atom labeling scheme for the non-hydrogen atoms. The thermal ellipsoids are scaled to enclose 50% probability.

Intrigued by the formation of the six-membered azanickelacycle **8a**, we explored the reactivity of the complex with our first reported ODC reaction conditions (Scheme 29). When 20 mol% of complex **8a** was substituted in place of $Ni(OAc)_2•4H_2O$, we discovered the ODC product **3z** and **3z'** were formed with almost identical yields from our reported work. Likewise, when a stoichiometric amount of **8a** was used, we noticed the diarylated ODC product **3z'** was formed in higher yields than **3z**. This could be due to slow protonation of the Ni–N bond allowing a second C–H activation to take place. Surprised by these data, complex **8a** could be undergoing a denitrogenation forming a Ni–C bond.

Scheme 29. Reactivity of complex **8a** under the nickel-catalyzed oxidative decarboxylative (hetero)arylation reaction conditions.



Reaction conditions: [a]Azanickelacycle **8a** (0.040 mmol), **1a** (0.16 mmol), heteroaromatic carboxylate **2a** (0.60 mmol), Ag_2CO_3 (2.0 equiv), Na_2CO_3 (4.0 equiv), and PivOH (1.5 equiv) in DMA (2 mL) for 24 h at 110 °C under a N_2 atmosphere. [b]Azanickelacycle **8a** (0.20 mmol), Heteroaromatic carboxylate **2a** (0.60 mmol), Ag_2CO_3 (2.0 equiv), Na_2CO_3 (4.0 equiv), and PivOH (1.5 equiv) in DMA (2 mL) for 24 h at 110 °C under a N_2 atmosphere. [c]^{1}H NMR yield with 1,3,5-trimethoxybenzene as an internal standard.

We hypothesized heating complex **8a** in different solvents would force **8a** to undergo denitrogenation, thereby creating the five-membered azanickelacycle. Heating of complex **8a** in DCM-d_2, MeCN-d_3, THF-d_8, or DMSO-d_6 showed no change in the starting material by ^{1}H NMR spectroscopy. Heating of **8a** in anhydrous DMA at 140 °C for 1 h led to a complex mixture of products. Upon switching the solvent to anhydrous DMF-d_7, we were able to see complex **8a** was converted to a new species. Heating of the six-membered azanickelacycle **8a** (red box outline), at 140 °C for 1 h led to formation of a new unknown product (Figure 3). Heating of the reaction over time and increasing temperature led to the formation of new unknown products. However, over time, there was a decrease in yield of the new product from 62 % to 37 %. Attempts to isolate the unknown product after 1 h were unsuccessful.

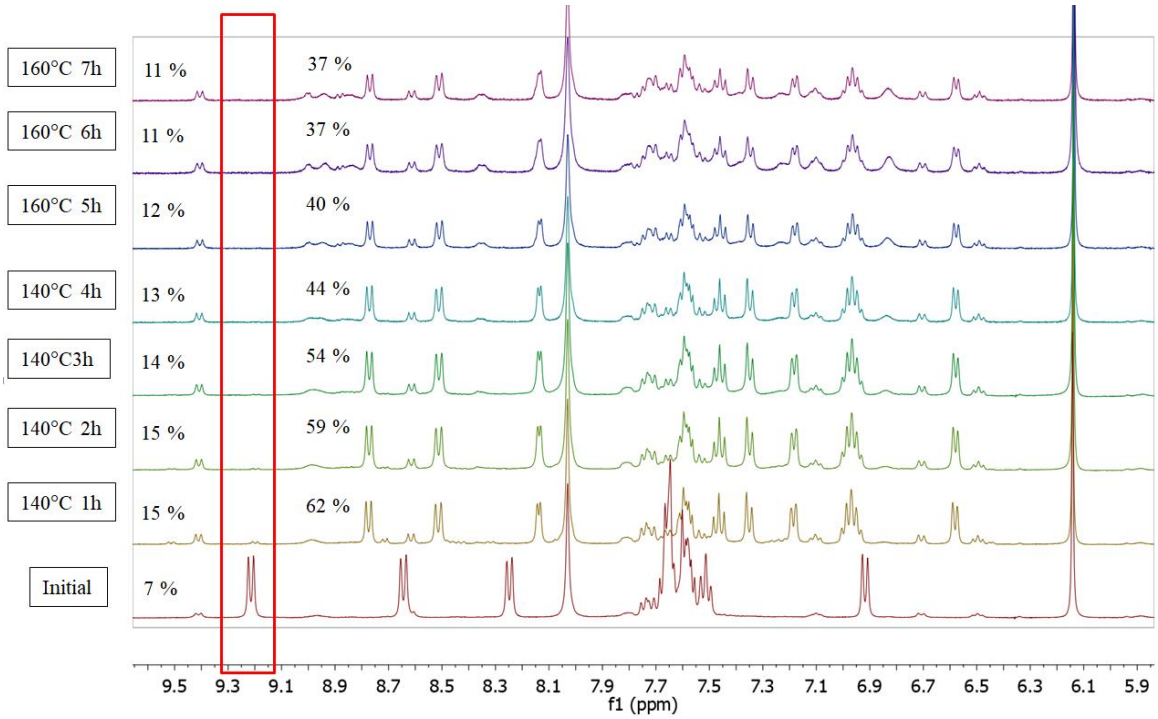
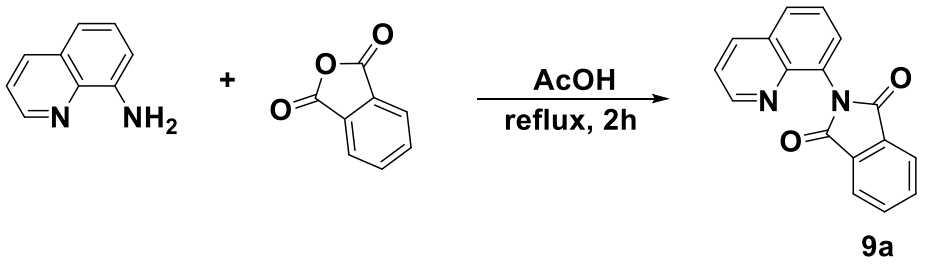


Figure 3. Heating of **8a** in DMF-d_7: Reaction conditions: **8a** (0.015 mmol) in DMF-d_7 (0.90 mL) with 1,3,5-trimethoxybenzene as an internal standard at 140 °C to 160 °C.

4.2.2. Synthesis of the Ni(II) Metallacycle by Decarbonylation of Phthalimides

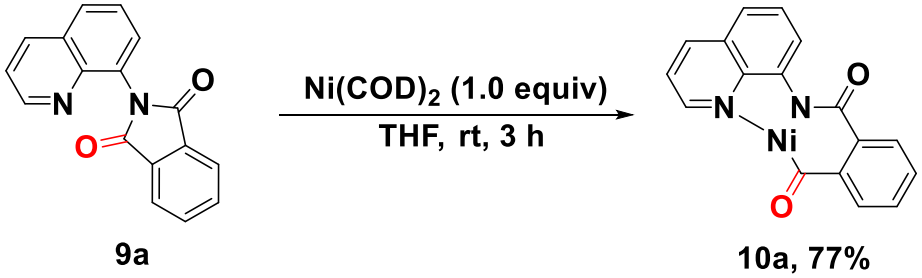
To obtain the desired five-membered azanickelacycle, we then tried a different synthetic route, decarbonylation of phthalimides. The 2-(quinolin-8-yl)-2,3-dihydro-1H-isoindole-1,3-dione was synthesized from a reported procedure.[98] Phthalic anhydride and 8-aminoquinoline were refluxed in acetic acid for 2 h, providing 79% yield of **9a** following recrystallization (Scheme 30). The phthalimide was found to be soluble in THF, MeCN, and $PhCH_3$ allowing for potential synthesis of the desired Ni(II) metallacycle.



Scheme 30. Synthesis of 2-(quinolin-8-yl)-2,3-dihydro-1H-isoindole-1,3-dione (**9a**) from 8-aminoquinoline and phthalic anhydride.

The reaction of 2-(quinolin-8-yl)-2,3-dihydro-1H-isoindole-1,3-dione (**9a**) was treated with equimolar amounts of $Ni(COD)_2$ in THF at room temperature. Coordination of the phthalimide to nickel is signaled by a change in color in the solution from clear to dark red. After stirring for 3 h, the mixture produced a light red precipitate that was filtered out of solution in (Scheme 31). The ^{1}H NMR spectrum of **10a** shows eight inequivalent aryl resonances adding up to ten protons. The $^{13}C\{^{1}H\}$ NMR spectrum shows fifteen different aryl resonances and two carbonyl resonance. The carbonyl resonance at δ 167.23 is indicative of a typical six-membered Ni(II) metallacycle while the second carbonyl resonance at δ 268.82 is from insertion of $Ni(COD)_2$ into the (O)C–N bond.[99]

Scheme 31. Synthesis of an azaacylNi(II) complex (**10a**) from insertion of nickel into the phthalimide C–N bond.[a]

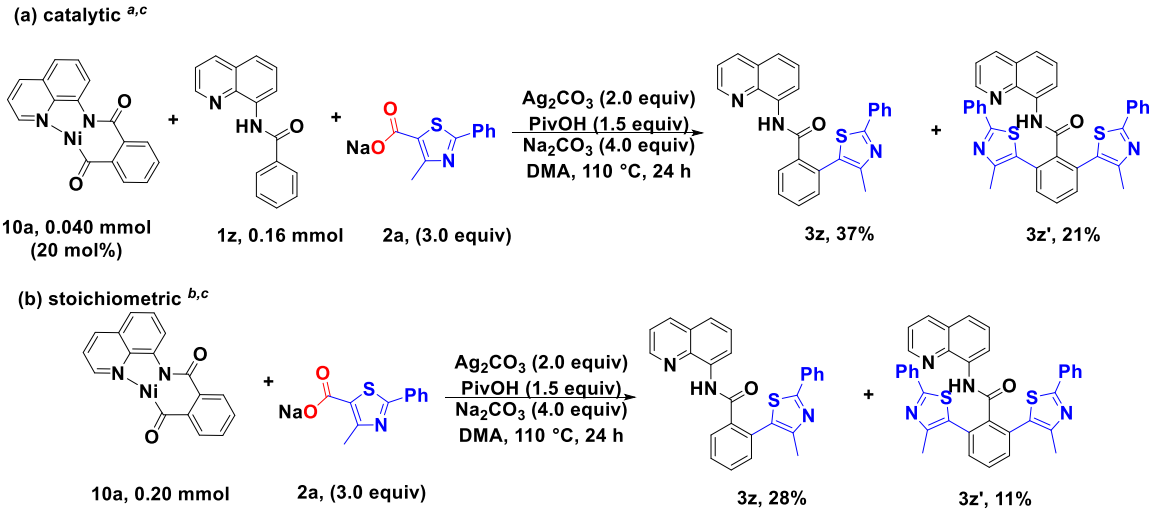


[a]Isolated yields. Reaction conditions: **9a** (1.0 mmol), $Ni(COD)_2$ (1.0 mmol) in THF (27 mL).

Complex **10a** was tested under our nickel-catalyzed ODC reaction conditions to see if it had similar reactivity as complex **8a** (Scheme 32). When 20 mol% of complex **10a** was substituted in place of $Ni(OAc)_2{\bullet}4H_2O$, we found the ODC products **3z** and **3z'** were formed in 37% and 21% yields. When a stoichiometric amount of complex **10a** was used, there was a higher yield of the monoarylation ODC product **3z** in 28% than the

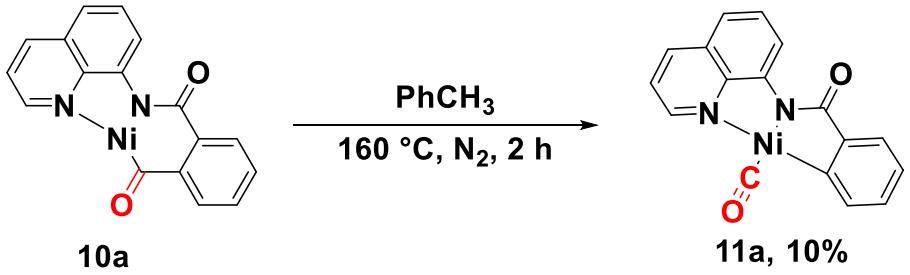
diarylation ODC product **3z'** in 11% yield. While complex **10a** shows reactivity under our reaction conditions, we were surprised to see differences in yields of **3z** and **3z'** between complex **8a** and **10a**.

Scheme 32. Reactivity of azaacylNi(II) complex **10a** under the nickel-catalyzed oxidative decarboxylative (hetero)arylation reaction conditions.



Reaction conditions: [a]Azanickelacycle **10a** (0.040 mmol), **1a** (0.16 mmol), heteroaromatic carboxylate **2a** (0.60 mmol), Ag_2CO_3 (2.0 equiv), Na_2CO_3 (4.0 equiv), and PivOH (1.5 equiv) in DMA (2 mL) for 24 h at 110 °C under a N_2 atmosphere. [b]Azanickelacycle **10a** (0.20 mmol), heteroaromatic carboxylate **2a** (0.60 mmol), Ag_2CO_3 (2.0 equiv), Na_2CO_3 (4.0 equiv), and PivOH (1.5 equiv) in DMA (2 mL) for 24 h at 110 °C under a N_2 atmosphere. [c]^{1}H NMR yield with 1,3,5-trimethoxybenzene as an internal standard.

With the azaacylNi(II) complex **10a** in hand, we hypothesized the metallacycle would undergo decarbonylation at an elevated temperature. Heating complex **10a** in MeCN, dioxane, DMC, or THF led to decomposition with no formation of the desired product **11a**. However, when complex **10a** was heated in $PhCH_3$, the solution turned from bright red to light yellow (see experimental below). Crystallization of the reaction mixture after heating afforded complex **11a** as bright yellow parallelepiped crystals (Scheme 33).



Scheme 33. Decarbonylation of the azaacylNi(II) metallacycle **10a** to complex **11a**.

The ^{1}H NMR spectrum of **11a** shows nine inequivalent aryl resonances adding up to ten protons. The ^{13}C{^{1}H} NMR spectrum shows fifteen different aryl resonances and one carbonyl resonance. The carbonyl resonance at δ 186.96 is indicative of a typical five-membered azanickel metallacycle.[89] The reaction mixture was allowed to cool to room temperature after heating affording complex **11a** as bright yellow crystals. FTIR of complex **11a** showed a characteristic carbonyl stretch at 2063 cm^{-1}. The structure of **11a** was established by single-crystal X-ray analysis to contain a square planar Ni(II) molecule (Figure 4)

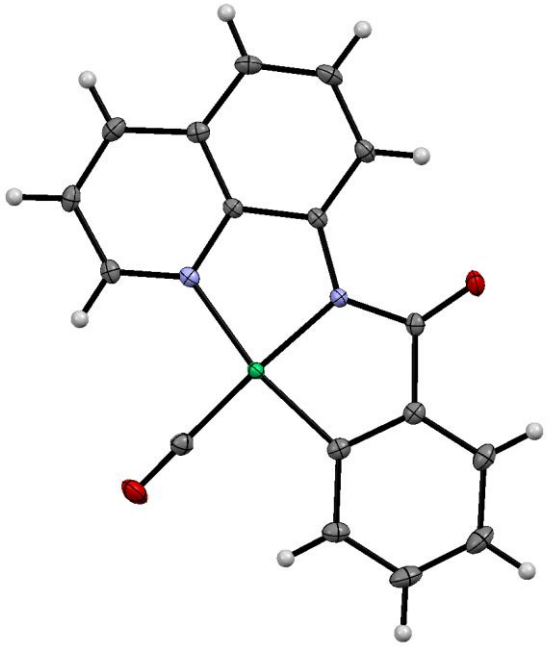
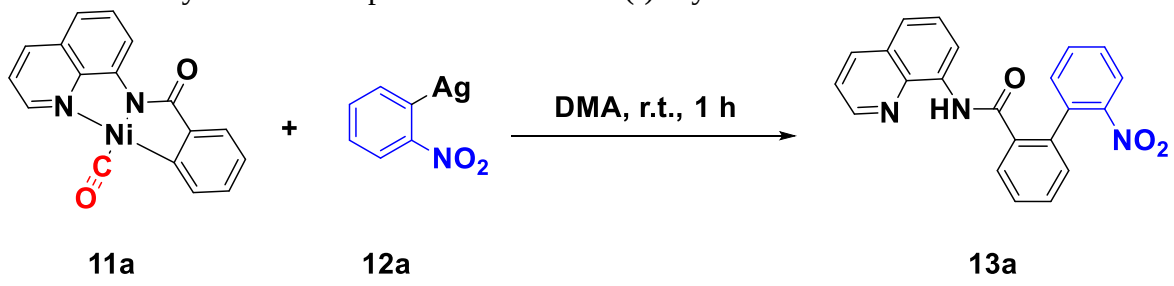


Figure 4. Perspective view of the molecular structure of $(C_{16}H_{10}N_2O)Ni(CO)$ (**11a**) with the atom labeling scheme for the non-hydrogen atoms. The thermal ellipsoids are scaled to enclose 50% probability.

After isolation of the new Ni(II) metallacycle, we wanted to probe our proposed catalytic cycle. We hypothesized in the previous chapters that silver is likely responsible for the decarboxylation step generating a well-defined silver aryl in solution, which then reactions with a nickel(II) metallacycle. To explore the possibility of such pathway, we conducted an experiment where complex **11a** was treated with equimolar amounts of (2-nitrophenyl)silver(I) in DMA (Scheme 34). The initial reaction solution turned from orange/yellow to dark when the (2-nitrophenyl)silver(I) solution was added dropwise. The reaction was allowed to stir for 1 h at room temperature. After extraction of the reaction mixture, we were excited to see **13a** was formed in 46% yield by ^{1}H NMR spectroscopy. When two equivalents of **12a** were added, the yield of **13a** increased to 68% (Scheme 34, entry 2). This transformation could be going through a transmetalation of the aryl fragment from Ag to Ni followed by concomitant oxidation of the nickel center to thereby generation the new C–C bond. This data suggest there could be

cooperation between both nickel and silver allowing for the remarkable efficiency and selectivity of our catalyst system as mentioned previously.

Scheme 34. Arylation of complex **11a** with silver(I)-aryl for C–C bond formation.[a]



11a **12a** **13a**

entry	(**12a**) Equivalence	yield (**13a**)[b]
1	1.0	46%
2	2.0	68%

[a]Reaction conditions: **11a** (0.025 mmol), **12a** (0.025 mmol or 0.050 mmol), in DMA (2 mL) for 1 h at room temperature under a N_2 atmosphere. [b1]H NMR yield with 1,3,5-trimethoxybenzene as an internal standard.

4.3. Conclusion

In conclusion, we have synthesized a catalytically relevant five-membered azanickelacycle by decarbonylation of an azaacylNi(II) complex (**10a**). The attempted denitrogenation of 3-(quinolin-8-yl)-3,4-dihydro-1,2,3-benzotriazin-4-one (**6a**) afforded an interesting nickel metallacycle dimer, that showed reactivity under our earlier reported reaction conditions. Ultimately, the five-membered Ni(II) complex (**11a**) showed reactivity with (2-nitrophenyl)silver(I) to form the arylated product (**13a**). These findings support that both metals are needed to form the desired ODC product.

4.4. Experimental

General Considerations. All manipulations were performed using standard Schlenk or glovebox techniques under a nitrogen atmosphere. All solvents (including dry DMA) were purchased from Alfa-Aesar and Fisher and used as received. All other reagents were purchased from Maybridge, Oakwood, Acros, Alfa-Aesar, and Strem and used without further purification. All NMR spectra were recorded at ambient temperature on an Agilent 400 MHz or JEOL 400 MHz (^{1}H, 400 MHz; ^{13}C{^{1}H}, 100 MHz) spectrometer. Chemical shifts are referenced to the residual solvent signals ($CDCl_3$: 7.26 ppm (^{1}H) and 77.2 ppm (^{13}C), DMSO-d_6: 2.50 ppm (^{1}H) and 39.5 ppm (^{13}C), CD_2Cl_2: 5.32 ppm (^{1}H) and 54.0 ppm (^{13}C)).[45] IR spectra were recorded on a PerkinElmer (Spectrum 100) FT-IR spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Column chromatography was performed using Silicycle Silica Flash P60 silica gel.

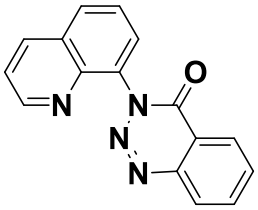
Synthesis of 3-(quinolin-8-yl)-3,4-dihydro-1,2,3-benzotriazin-4-one (**6a**).

Amide bond formation. A 100 mL two-neck round bottom flask was charged with 8-aminoquinoline (1.44 g, 10.0 mmol), Et_3N (1.56 mL, 12.0 mmol), and methylene chloride (20 mL) under a N_2 atmosphere. The corresponding 2-nitrobenzoyl chloride (1.58 mL, 12.0 mmol) was added dropwise at room temperature over 10 minutes. The mixture was stirred overnight at room temperature. The reaction was quenched with 10 mL of saturated $NaHCO_3$ and extracted with methylene chloride (3 x 25 mL). The combined organic layer was washed with brine (15 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified via silica gel column chromatography (gradient elution, hexanes : ethyl acetate (5:1, v/v) to (1:1, v/v)) yielding 2-nitro-*N*-(quinolin-8-yl)benzamide.

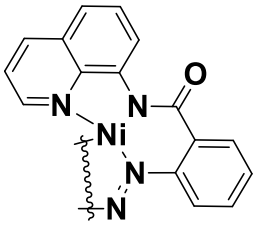
Reduction of 2-nitro-*N*-(quinolin-8-yl)benzamide. A 50 mL round bottom flask was charged with water (5 mL), iron powder (10.0 mmol, 558 mg), and concentrated HCl (1.5 drops) were added to a solution of 2-nitro-*N*-(quinolin-8-yl)benzamide (1.00 mmol, 293 mg) in THF (15 mL). The mixture was refluxed for 3 h. Upon completion, the reaction

mixture was allowed to cool to room temperature, diluted with brine (25 mL) and filtered through a pad of celite. The filtrate was extracted with ethyl acetate (3 x 25 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified via silica gel column chromatography (gradient elution, hexanes : ethyl acetate (19:1, v/v) to (10:1, v/v)) yielding 2-amino-*N*-(quinolin-8-yl)benzamide.

Annulation of 2-amino-*N*-(quinolin-8-yl)benzamide. A oven dried Schlenk tube (50 mL) was charged with 2-amino-*N*-(quinolin-8-yl)benzamide (3.00 mmol, 790 mg), TBAI (0.15 mmol, 55.4 mg), *tert*-butyl nitrite (9.00 mmol, 1.07 mL), and MeCN (30 mL). The Schlenk tube was sealed with a rubber septum and placed in a pre-heated oil bath at 60 °C for 12 h. The solution was cooled to room temperature and solvent was removed under reduced pressure. The residue was purified via silica gel column chromatography (gradient elution, hexanes : ethyl acetate (1:1, v/v) to (1:2, v/v)) yielding 3-(quinolin-8-yl)-3,4-dihydro-1,2,3-benzotriazin-4-one (6a) in 50% (1.50 mmol, 417 mg).

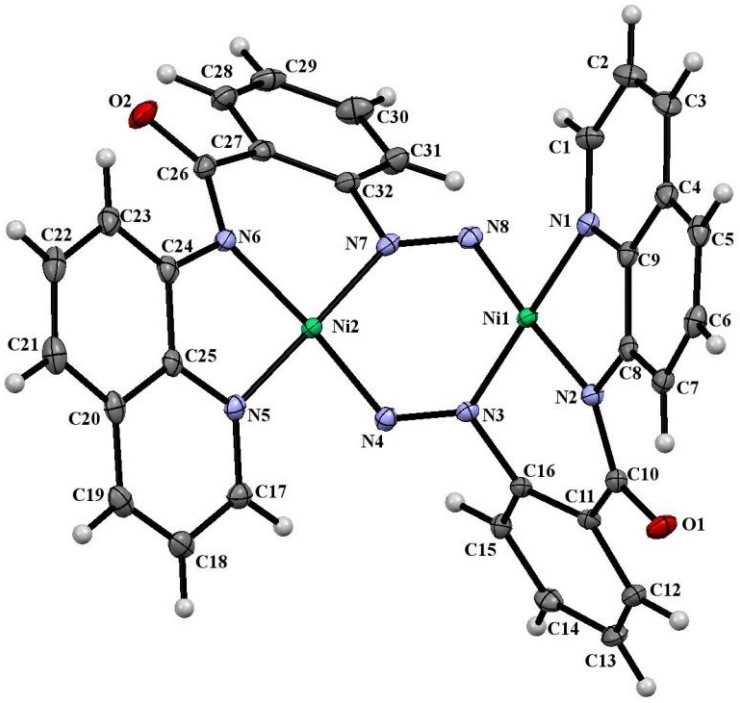


3-(quinolin-8-yl)-3,4-dihydro-1,2,3-benzotriazin-4-one (**6a**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.57 (dd, *J* = 8.4, 1.7 Hz, 1H), 8.35 (dddd, *J* = 8.0, 4.7, 1.4, 0.6 Hz, 2H), 8.27 (dd, *J* = 8.3, 1.4 Hz, 1H), 8.20 (ddd, *J* = 8.1, 7.3, 1.4 Hz, 1H), 8.13 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.03 (ddd, *J* = 8.0, 7.3, 1.2 Hz, 1H), 7.86 (dd, *J* = 8.3, 7.3 Hz, 1H), 7.66 (dd, *J* = 8.3, 4.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 155.13, 151.50, 143.57, 143.21, 136.55, 136.17, 135.83, 133.41, 130.39, 129.35, 128.64, 128.32, 126.40, 124.94, 122.42, 119.94. The spectral data is consistent with literature.[28]



[($C_{16}H_{10}N_4O$)Ni]$_2$ (**8a**). In a glovebox filled with N_2. A mixture of 3-(quinolin-8-yl)-3,4-dihydro-1,2,3-benzotriazin-4-one (54.8 mg, 0.200 mmol) was added to a 20 mL vial and dissolved in THF (4 mL). In another 20 mL vial, Ni(COD)$_2$ (55.0 mg, 0.200 mmol) and ligand (0.200 mmol) was dissolved in THF (4 mL). The solution of Ni(COD)$_2$ was added dropwise to the vial containing 3-(quinolin-8-yl)-3,4-dihydro-1,2,3-benzotriazin-4-one and THF over 5 minutes. The solution was allowed to stir for 3 h at room temperature. The volume was then reduced to ~1.5 mL and added dropwise to hexanes (~100 mL) to precipitate out a dark brown solid. The solid was then dried under vacuum to give 47.2 mg (0.142 mmol, 71%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 9.17 (dd, *J* = 7.9, 1.1 Hz, 2H), 8.30 (dd, *J* = 8.3, 1.5 Hz, 2H), 8.25 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.60 (t, *J* = 8.0 Hz, 2H), 7.56 – 7.47 (m, 4H), 7.44 – 7.33 (m, 4H), 7.27 (dd, *J* = 8.2, 5.1 Hz, 2H), 6.78 (dd, *J* = 7.9, 1.2 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, CD_2Cl_2) δ 167.03, 151.78, 149.18, 147.96, 144.85, 139.86, 131.53, 130.92, 130.56, 130.12, 130.08, 129.27, 122.84, 121.85, 119.71, 119.14.

Heating of [($C_{16}H_{10}N_4O$)Ni]$_2$ (8a) in J. Young NMR tube. In a glovebox filled with N_2. A J. Young NMR tube was charged with azanickelacycle **8a** (5.0 mg, 0.015 mmol), 1,3,5-trimethoxybenzene (1.3 mg, 0.0077 mmol), and DMF-d_7 (0.90 mL). The J. Young NMR tube was taken out of the glovebox and placed in a preheated oil bath at 140 °C. The reaction was monitored by ^{1}H NMR every hour. After 4 h, the oil bath was heated to 160 °C and monitored by ^{1}H NMR every hour.



Perspective view of the molecular structure of $[(C_{16}H_{10}N_4O)Ni]_2$ (**8a**) with the atom labeling scheme for the non-hydrogen atoms. The thermal ellipsoids are scaled to enclose 50% probability. The Ni(1)···Ni(2) interatomic distance is 3.285 Å. The acute dihedral angle between the plane containing atoms Ni(1), N(1), N(2), N3), N(8) and the plane containing atoms Ni(2), N(4), N5), N(6), N(7) is 77.2º.

Description of the X-ray Structural Analysis of $[(C_{16}H_{10}N_4O)Ni]_2.CH_2Cl_2$ (8a)

A dark brown parallelepiped crystal of $[(C_{16}H_{10}N_4O)Ni]_2.CH_2Cl_2$ (**8a**) was coated in polybutene oil (Sigma-Aldrich) and placed on the end of a MiTeGen loop. The sample was cooled to 100 K with an Oxford Cryostream 700 system and optically aligned on a Bruker AXS D8 Venture fixed-chi X-ray diffractometer equipped with a Triumph monochromator, a Mo Kα radiation source (λ = 0.71073 Å), and a PHOTON 100 CMOS detector. Three sets of 12 frames each were collected using the omega scan method with a 10 second exposure time. Integration of these frames followed by reflection indexing and least-squares refinement produced a crystal orientation matrix for the monoclinic crystal lattice that was used for the structural analysis.

Data collection consisted of the measurement of a total of 1056 frames in four runs using omega scans with the detector held at 5.00 cm from the crystal. Frame scan parameters are summarized below:

Data collection details for $[(C_{16}H_{10}N_4O)Ni]_2 \cdot CH_2Cl_2$ (8a).

Run	2θ	ω	φ	χ	Scan Width (°)	Frames	Exposure Time (sec)
1	11.01	-171.48	144.00	54.74	0.70	264	60.00
2	11.01	-171.48	72.00	54.74	0.70	264	60.00
3	11.01	-171.48	-144.00	54.74	0.70	264	60.00
4	11.01	-171.48	0.00	54.74	0.70	264	60.00

The APEX3 software program (version 2016.9-0)[100] was used for diffractometer control, preliminary frame scans, indexing, orientation matrix calculations, least-squares refinement of cell parameters, and the data collection. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 58425 reflections to a maximum θ angle of 27.98° (0.76 Å resolution), of which 7038 were independent (average redundancy 8.301, completeness = 98.4%, R_{int} = 6.17%, R_{sig} = 4.35%) and 5358 (76.13%) were greater than $2\sigma(F^2)$. The final cell constants of a = 12.1353(10) Å, b = 24.815(2) Å, c = 10.1263(9) Å, β = 103.132(2)°, volume = 2969.7(4) $Å^3$, are based upon the refinement of the XYZ-centroids of 9287 reflections above 20 σ(I) with 6.174° < 2θ < 54.87°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.850. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.437 and 0.922.

The structure was solved by direct methods and difference Fourier analyses using the programs provided by SHELXL-2014/7.[101] Idealized positions for the methylene and aromatic hydrogen atoms were included as fixed contributions using a riding model with isotropic temperature factors set at 1.2 times that of the adjacent carbon atom. Full-matrix least-squares refinement, based upon the minimization of $\Sigma w_i |F_o^2 - F_c^2|^2$, with weighting

$w_i^{-1} = [\sigma^2(F_o^2) + (0.0203\ P)^2 + 2.9372\ P]$, where $P = (\text{Max}\ (F_o^2, 0) + 2\ F_c^2)/3.$[2] The final anisotropic full-matrix least-squares refinement on F^2 with 424 variables converged at R1 = 3.06 % for the 5358 data with $I>2\sigma(I)$ and wR2 = 5.58 % for all data. The goodness-of-fit was 1.016.[102]

A correction for secondary extinction was not applied. The largest peak in the final difference electron density synthesis was 0.399 $e^-/Å^3$ and the largest hole was -0.545 $e^-/Å^3$ with an RMS deviation of 0.079 $e^-/Å^3$. The linear absorption coefficient, atomic scattering factors, and anomalous dispersion corrections were calculated from values found in the International Tables of X-ray Crystallography.[103]

Crystal data for $[(C_{16}H_{10}N_4O)Ni]_2 \cdot CH_2Cl_2$ (8a).

Ident. code	jh53cms	
Chem. form.	$C_{33}H_{22}Cl_2N_8Ni_2O_2$	
Mol. weight	750.90 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.055 x 0.111 x 0.663 mm	
Cryst. type	monoclinic	
Space group	$P2_1/c$ (No. 14)	
Unit cell	a = 12.1353(10) Å	α = 90°
	b = 24.815(2) Å	β = 103.132(2)°
	c = 10.1263(9) Å	γ = 90°
Volume, $Å^3$	2969.7(4)	
Z	4	
Density (calc)	1.679 g/cm^3	
Abs. coeff.	1.497 mm^{-1}	
F(000)	1528	

Data collection and structure refinement for $[(C_{16}H_{10}N_4O)Ni]_2 \cdot CH_2Cl_2$ (**8a**).

Theta range	2.88 to 27.98°	
Index ranges	$-15 \leq h \leq 15$, $-32 \leq k \leq 32$, $-13 \leq l \leq 13$	
Reflections	58425	
Independent refls	7038 [R(int) = 0.0617]	
Coverage	98.4%	
Abs. correction	multi-scan	
Max./ min. trans.	0.922 and 0.437	
Refinement method	Full-matrix least-squares on F^2	
Ref. program	SHELXL-2014/7 (Sheldrick, 2014)	
Data / restrs / parms	7038 / 0 / 424	
GOF on F^2	1.016	
Final R indices	5358 data; $I>2\sigma(I)$	R1 = 0.0306, wR2 = 0.0587
	all data	R1 = 0.0558, wR2 = 0.0655
Largest diff. peak and hole	0.399 and -0.545 $e^-/Å^3$	

Atomic coordinates and equivalent isotropic atomic displacement parameters ($Å^2$) for $[(C_{16}H_{10}N_4O)Ni]_2 \cdot CH_2Cl_2$ (8a). U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U(eq)
Ni1	0.48714(2)	0.20781(2)	0.38695(3)	0.01089(7)
Ni2	0.21247(2)	0.18842(2)	0.29789(3)	0.01136(7)
O1	0.63111(13)	0.34317(6)	0.26545(15)	0.0183(3)

	x/a	y/b	z/c	U(eq)
O2	0.05756(13)	0.04119(6)	0.24573(16)	0.0232(4)
N1	0.59986(14)	0.15761(7)	0.36212(17)	0.0134(4)
N2	0.56869(14)	0.25817(6)	0.30274(17)	0.0120(4)
N3	0.37741(14)	0.25818(6)	0.40015(17)	0.0113(3)
N4	0.27252(14)	0.25286(7)	0.36729(17)	0.0128(4)
N5	0.11739(14)	0.22296(7)	0.14396(17)	0.0133(4)
N6	0.13645(14)	0.12434(7)	0.22252(18)	0.0130(4)
N7	0.31233(14)	0.15094(6)	0.43374(17)	0.0121(4)
N8	0.41704(14)	0.15655(7)	0.46962(17)	0.0133(4)
C1	0.61749(18)	0.10772(8)	0.4094(2)	0.0173(5)
C2	0.69670(19)	0.07351(9)	0.3707(2)	0.0227(5)
C3	0.75627(19)	0.09119(9)	0.2793(2)	0.0203(5)
C4	0.73955(18)	0.14411(8)	0.2266(2)	0.0161(4)
C5	0.79267(18)	0.16575(9)	0.1272(2)	0.0172(5)
C6	0.77024(18)	0.21788(9)	0.0860(2)	0.0175(5)
C7	0.69883(17)	0.25184(8)	0.1413(2)	0.0142(4)
C8	0.64308(17)	0.23187(8)	0.2360(2)	0.0126(4)
C9	0.66175(17)	0.17688(8)	0.2744(2)	0.0132(4)
C10	0.57337(17)	0.31253(8)	0.3178(2)	0.0130(4)
C11	0.50696(17)	0.33581(8)	0.4138(2)	0.0121(4)
C12	0.53571(18)	0.38774(8)	0.4635(2)	0.0152(4)
C13	0.48073(18)	0.41252(8)	0.5530(2)	0.0162(4)
C14	0.39442(18)	0.38582(8)	0.5957(2)	0.0163(4)
C15	0.36168(17)	0.33496(8)	0.5447(2)	0.0137(4)
C16	0.41704(17)	0.31082(8)	0.4546(2)	0.0120(4)

	x/a	y/b	z/c	U(eq)
C17	0.10322(18)	0.27529(8)	0.1189(2)	0.0155(4)
C18	0.03540(18)	0.29448(9)	0.9969(2)	0.0180(5)
C19	0.98563(18)	0.25885(9)	0.8980(2)	0.0186(5)
C20	0.00015(17)	0.20288(9)	0.9207(2)	0.0164(4)
C21	0.95287(18)	0.16230(9)	0.8261(2)	0.0206(5)
C22	0.97150(18)	0.10920(10)	0.8610(2)	0.0213(5)
C23	0.03199(17)	0.09301(9)	0.9907(2)	0.0183(5)
C24	0.07803(17)	0.13135(8)	0.0865(2)	0.0149(4)
C25	0.06506(16)	0.18645(8)	0.0480(2)	0.0131(4)
C26	0.11679(17)	0.08050(8)	0.2926(2)	0.0154(4)
C27	0.16762(17)	0.08165(8)	0.4435(2)	0.0150(4)
C28	0.11652(19)	0.04896(8)	0.5241(2)	0.0191(5)
C29	0.15311(19)	0.04724(9)	0.6637(2)	0.0211(5)
C30	0.2482(2)	0.07672(9)	0.7260(2)	0.0230(5)
C31	0.30268(19)	0.10861(9)	0.6482(2)	0.0195(5)
C32	0.26091(17)	0.11193(8)	0.5090(2)	0.0136(4)
C33	0.7187(2)	0.46528(9)	0.2612(2)	0.0245(5)
Cl1	0.59581(6)	0.49793(3)	0.16820(7)	0.03478(16)
Cl2	0.75204(5)	0.48583(2)	0.43372(6)	0.02809(14)

Interatomic distances (Å) for $[(C_{16}H_{10}N_4O)Ni]_2{\cdot}CH_2Cl_2$ (**8a**).

Ni1-N8	1.8347(17)	Ni1-N3	1.8531(17)
Ni1-N1	1.9086(17)	Ni1-N2	1.9109(17)
Ni2-N4	1.8301(17)	Ni2-N7	1.8624(17)
Ni2-N6	1.9085(16)	Ni2-N5	1.9179(17)

O1-C10	1.233(2)	O2-C26	1.240(2)
N1-C1	1.327(3)	N1-C9	1.373(3)
N2-C10	1.357(3)	N2-C8	1.405(3)
N3-N4	1.247(2)	N3-C16	1.456(2)
N5-C17	1.327(3)	N5-C25	1.374(3)
N6-C26	1.349(3)	N6-C24	1.409(3)
N7-N8	1.247(2)	N7-C32	1.457(3)
C1-C2	1.404(3)	C2-C3	1.370(3)
C3-C4	1.415(3)	C4-C9	1.412(3)
C4-C5	1.419(3)	C5-C6	1.367(3)
C6-C7	1.413(3)	C7-C8	1.384(3)
C8-C9	1.423(3)	C10-C11	1.511(3)
C11-C16	1.397(3)	C11-C12	1.399(3)
C12-C13	1.385(3)	C13-C14	1.389(3)
C14-C15	1.387(3)	C15-C16	1.386(3)
C17-C18	1.403(3)	C18-C19	1.369(3)
C19-C20	1.412(3)	C20-C25	1.409(3)
C20-C21	1.418(3)	C21-C22	1.370(3)
C22-C23	1.410(3)	C23-C24	1.383(3)
C24-C25	1.421(3)	C26-C27	1.513(3)
C27-C28	1.392(3)	C27-C32	1.394(3)
C28-C29	1.383(3)	C29-C30	1.391(3)
C30-C31	1.386(3)	C31-C32	1.388(3)
C33-Cl1	1.769(2)	C33-Cl2	1.776(2)

Bond angles (°) for $[(C_{16}H_{10}N_4O)Ni]_2{\cdot}CH_2Cl_2$ (8a).

N8-Ni1-N3	91.11(7)	N8-Ni1-N1	91.61(7)
N3-Ni1-N1	176.39(7)	N8-Ni1-N2	176.23(7)
N3-Ni1-N2	92.56(7)	N1-Ni1-N2	84.77(7)
N4-Ni2-N7	90.99(7)	N4-Ni2-N6	174.70(7)
N7-Ni2-N6	93.07(7)	N4-Ni2-N5	92.02(7)
N7-Ni2-N5	173.64(7)	N6-Ni2-N5	84.29(7)
C1-N1-C9	119.44(18)	C1-N1-Ni1	128.53(15)
C9-N1-Ni1	111.82(13)	C10-N2-C8	120.05(17)
C10-N2-Ni1	127.76(14)	C8-N2-Ni1	111.43(13)
N4-N3-C16	115.16(16)	N4-N3-Ni1	128.01(14)
C16-N3-Ni1	116.83(13)	N3-N4-Ni2	119.21(14)
C17-N5-C25	119.41(18)	C17-N5-Ni2	128.36(15)
C25-N5-Ni2	112.10(13)	C26-N6-C24	120.24(17)
C26-N6-Ni2	126.06(15)	C24-N6-Ni2	112.21(13)
N8-N7-C32	116.80(17)	N8-N7-Ni2	127.46(14)
C32-N7-Ni2	115.72(13)	N7-N8-Ni1	119.45(14)
N1-C1-C2	121.8(2)	C3-C2-C1	119.7(2)
C2-C3-C4	120.0(2)	C9-C4-C3	117.06(19)
C9-C4-C5	118.19(19)	C3-C4-C5	124.7(2)
C6-C5-C4	118.9(2)	C5-C6-C7	122.7(2)
C8-C7-C6	120.10(19)	C7-C8-N2	129.43(19)
C7-C8-C9	117.39(18)	N2-C8-C9	113.18(17)
N1-C9-C4	121.86(18)	N1-C9-C8	115.74(18)
C4-C9-C8	122.39(19)	O1-C10-N2	125.29(19)
O1-C10-C11	118.64(18)	N2-C10-C11	115.96(17)
C16-C11-C12	116.79(19)	C16-C11-C10	125.93(18)

C12-C11-C10	117.26(18)	C13-C12-C11	121.8(2)
C12-C13-C14	120.09(19)	C15-C14-C13	119.37(19)
C16-C15-C14	119.86(19)	C15-C16-C11	122.04(18)
C15-C16-N3	117.96(17)	C11-C16-N3	119.98(18)
N5-C17-C18	121.7(2)	C19-C18-C17	119.9(2)
C18-C19-C20	119.9(2)	C25-C20-C19	117.17(19)
C25-C20-C21	117.9(2)	C19-C20-C21	124.9(2)
C22-C21-C20	119.4(2)	C21-C22-C23	122.3(2)
C24-C23-C22	120.0(2)	C23-C24-N6	129.3(2)
C23-C24-C25	117.9(2)	N6-C24-C25	112.79(18)
N5-C25-C20	121.90(19)	N5-C25-C24	115.81(18)
C20-C25-C24	122.27(19)	O2-C26-N6	126.1(2)
O2-C26-C27	117.97(19)	N6-C26-C27	115.84(17)
C28-C27-C32	117.2(2)	C28-C27-C26	116.58(19)
C32-C27-C26	126.21(18)	C29-C28-C27	122.3(2)
C28-C29-C30	119.2(2)	C31-C30-C29	119.7(2)
C30-C31-C32	120.0(2)	C31-C32-C27	121.36(19)
C31-C32-N7	118.01(18)	C27-C32-N7	120.50(18)
Cl1-C33-Cl2	111.59(12)		

Anisotropic atomic displacement parameters ($Å^2$) for $[(C_{16}H_{10}N_4O)Ni]_2 \cdot CH_2Cl_2$ (8a). The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$.

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Ni1	0.01075(13)	0.00827(12)	0.01414(14)	0.0004(1)	0.00386(10)	-0.0005(1)
Ni2	0.01095(13)	0.00888(12)	0.01419(14)	-0.0003(1)	0.00273(10)	-0.0015(1)

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	0.0212(8)	0.0122(7)	0.0247(9)	0.0004(6)	0.0120(7)	-0.0041(6)
O2	0.0255(9)	0.0155(8)	0.0276(9)	-0.0030(7)	0.0037(7)	-0.0093(7)
N1	0.0125(9)	0.0124(8)	0.0144(9)	-0.0011(7)	0.0014(7)	-0.0013(7)
N2	0.0126(9)	0.0107(8)	0.0132(9)	0.0000(7)	0.0042(7)	-0.0001(7)
N3	0.0122(9)	0.0099(8)	0.0122(9)	0.0005(7)	0.0035(7)	-0.0012(7)
N4	0.0125(9)	0.0130(8)	0.0131(9)	0.0005(7)	0.0031(7)	-0.0017(7)
N5	0.0103(9)	0.0147(9)	0.0160(9)	0.0000(7)	0.0052(7)	-0.0014(7)
N6	0.0111(9)	0.0114(8)	0.0165(9)	-0.0020(7)	0.0028(7)	-0.0014(7)
N7	0.0140(9)	0.0095(8)	0.0141(9)	-0.0020(7)	0.0058(7)	-0.0025(7)
N8	0.0145(9)	0.0119(8)	0.0142(9)	-0.0020(7)	0.0049(7)	-0.0001(7)
C1	0.0187(11)	0.0130(10)	0.0200(12)	0.0025(9)	0.0040(9)	0.0007(8)
C2	0.0244(13)	0.0138(11)	0.0293(13)	0.0011(9)	0.0050(11)	0.0053(9)
C3	0.0169(11)	0.0162(11)	0.0277(13)	-0.0044(9)	0.0048(10)	0.0050(9)
C4	0.0129(10)	0.0159(10)	0.0185(11)	-0.0046(9)	0.0015(9)	-0.0010(8)
C5	0.0118(11)	0.0225(11)	0.0174(11)	-0.0062(9)	0.0035(9)	-0.0004(9)
C6	0.0143(11)	0.0235(12)	0.0156(11)	-0.0032(9)	0.0052(9)	-0.0047(9)
C7	0.0129(10)	0.0151(10)	0.0139(11)	-0.0007(8)	0.0014(9)	-0.0025(8)
C8	0.0099(10)	0.0154(10)	0.0112(10)	-0.0035(8)	-0.0002(8)	-0.0016(8)
C9	0.0123(10)	0.0144(10)	0.0125(10)	-0.0029(8)	0.0021(8)	-0.0019(8)
C10	0.0115(10)	0.0127(9)	0.0139(10)	0.0004(8)	0.0010(8)	-0.0007(8)
C11	0.0121(10)	0.0107(9)	0.0129(10)	0.0025(8)	0.0017(8)	0.0015(8)
C12	0.0159(11)	0.0105(10)	0.0183(11)	0.0006(8)	0.0018(9)	-0.0022(8)
C13	0.0189(11)	0.0097(10)	0.0188(11)	-0.0030(8)	0.0015(9)	-0.0006(8)
C14	0.0181(11)	0.0146(10)	0.0167(11)	-0.0023(8)	0.0049(9)	0.0038(8)
C15	0.0105(10)	0.0144(10)	0.0168(11)	0.0009(8)	0.0046(9)	-0.0010(8)

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C16	0.0122(10)	0.0094(9)	0.0135(10)	0.0013(8)	0.0008(8)	0.0000(8)
C17	0.0134(10)	0.0147(10)	0.0202(11)	0.0004(9)	0.0074(9)	-0.0011(8)
C18	0.0145(11)	0.0190(11)	0.0224(12)	0.0065(9)	0.0082(9)	0.0002(9)
C19	0.0133(11)	0.0257(12)	0.0181(11)	0.0066(9)	0.0060(9)	0.0018(9)
C20	0.0093(10)	0.0261(12)	0.0150(11)	-0.0001(9)	0.0049(9)	-0.0001(9)
C21	0.0130(11)	0.0328(13)	0.0159(11)	-0.0026(10)	0.0029(9)	-0.0009(9)
C22	0.0133(11)	0.0295(13)	0.0207(12)	-0.0097(10)	0.0029(9)	-0.0030(9)
C23	0.0112(10)	0.0202(11)	0.0238(12)	-0.0058(9)	0.0046(9)	-0.0002(9)
C24	0.0090(10)	0.0185(11)	0.0180(11)	-0.0023(9)	0.0047(9)	0.0008(8)
C25	0.0082(10)	0.0170(10)	0.0156(10)	-0.0012(9)	0.0058(8)	-0.0003(8)
C26	0.0117(10)	0.0128(10)	0.0227(12)	-0.0022(9)	0.0061(9)	-0.0010(8)
C27	0.0148(11)	0.0106(10)	0.0216(12)	-0.0001(8)	0.0083(9)	0.0017(8)
C28	0.0167(11)	0.0131(10)	0.0287(13)	0.0019(9)	0.0076(10)	-0.0021(9)
C29	0.0267(13)	0.0123(11)	0.0293(13)	0.0046(9)	0.0164(11)	0.0009(9)
C30	0.0334(14)	0.0188(11)	0.0186(12)	0.0022(9)	0.0099(10)	0.0000(10)
C31	0.0232(12)	0.0156(11)	0.0198(12)	0.0013(9)	0.0049(10)	-0.0032(9)
C32	0.0155(11)	0.0098(9)	0.0167(11)	0.0009(8)	0.0060(9)	-0.0003(8)
C33	0.0263(13)	0.0151(11)	0.0342(14)	-0.0012(10)	0.0111(11)	0.0023(9)
Cl1	0.0348(4)	0.0289(3)	0.0366(4)	-0.0098(3)	-0.0002(3)	0.0104(3)
Cl2	0.0267(3)	0.0210(3)	0.0350(3)	-0.0011(2)	0.0038(3)	-0.0063(2)

Hydrogen atom coordinates and isotropic atomic displacement parameters (Å^2) for [($C_{16}H_{10}N_4O$)Ni]$_2$.CH_2Cl_2 (8a).

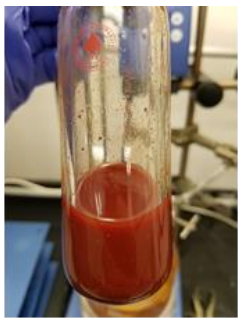
	x/a	y/b	z/c	U(eq)
H1	0.5753	0.0948	0.4713	0.021
H2	0.7089	0.0383	0.4077	0.027
H3	0.8088	0.0679	0.2513	0.024
H5	0.8430	0.1444	0.0898	0.021
H6	0.8041	0.2318	0.0173	0.021
H7	0.6890	0.2884	0.1136	0.017
H12	0.5945	0.4065	0.4352	0.018
H13	0.5021	0.4478	0.5852	0.019
H14	0.3581	0.4022	0.6593	0.02
H15	0.3014	0.3167	0.5714	0.016
H17	0.1399	0.3004	0.1853	0.019
H18	0.0240	0.3321	-0.0171	0.022
H19	-0.0586	0.2718	-0.1857	0.022
H21	-0.0913	0.1719	-0.2607	0.025
H22	-0.0574	0.0823	-0.2045	0.026
H23	0.0411	0.0558	0.0123	0.022
H28	0.0543	0.0271	0.4816	0.023
H29	0.1137	0.0262	0.7164	0.025
H30	0.2757	0.0750	0.8216	0.028
H31	0.3686	0.1282	0.6902	0.023
H33A	0.7832	0.4737	0.2198	0.029
H33B	0.7068	0.4258	0.2564	0.029

Synthesis of 2-(quinolin-8-yl)-2,3-dihydro-1H-isoindole-1,3-dione (9a). A round bottom flask was charged with phthalic anhydride (0.74 g, 5 mmol) and 8-aminoquinoline (0.72 g, 5 mmol). Acetic acid (30 mL) was added and the mixture was refluxed for 2 hours. The round bottom flask was allowed to cool to room temperature and an equal volume of water (30 mL) was added. The mixture was allowed to sit overnight and the solid was recovered by filtration. The solid was dried by high vacuum to yield 2-(quinolin-8-yl)-2,3-dihydro-1H-isoindole-1,3-dione in 987 mg (3.60 mmol, 72 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, *J* = 4.2 Hz, 1H), 8.24 (dd, *J* = 8.3, 1.5 Hz, 1H), 8.04 – 7.94 (m, 3H), 7.81 (ddd, *J* = 5.4, 3.1, 1.0 Hz, 2H), 7.76 (d, *J* = 7.3 Hz, 1H), 7.68 (t, *J* = 7.7 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.07, 151.05, 144.39, 136.45, 134.30, 132.62, 130.46, 129.88, 129.78, 129.47, 126.33, 123.99, 122.07. The spectral data is consistent with literature.[98]

Synthesis of intermediate (10a). In a N_2 filled glovebox, an over dried 20 mL vial with a stir bar was charged with phthalimide (**9a**) (274 mg, 1.00 mmol) and THF (20 mL). In an oven dried 100 mL RB flask was charged with THF (15 mL) and $Ni(COD)_2$. Both solutions were allowed to stir until starting materials were dissolved. The phthalimide containing solution was then added dropwise to the $Ni(COD)_2$ (275 mg, 1.00 mmol) solution while stirring vigorously. After complete addition of phthalimide solution, the reaction mixture was allowed to stir for 3 h at room temperature. After completion, the reaction mixture was filtered in a Buchner funnel with filter paper and washed with Et_2O (~50 mL). The filtrate was then added to a dried RB flask with Et_2O and allowed to sit over night to allow any remaining nickel metallacycle to crash out. The filtrate was filtered the following morning. The nickel metallacycle was then dried under vacuum for 2 h yielding **10a** in 256 mg as light red solid (0.77 mmol, 77%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 9.08 (d, *J* = 8.0 Hz, 1H), 8.45 (d, *J* = 7.9 Hz, 1H), 8.31 (d, *J* = 9.0 Hz, 1H), 7.95 (d, *J* = 4.2 Hz, 1H), 7.74 (t, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.50 – 7.38 (m, 3H), 7.33 (dd, *J* = 8.3, 4.9 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, CD_2Cl_2) δ 268.82, 167.23, 148.98, 147.47, 143.44, 139.60, 139.55, 138.20, 138.16, 134.01, 131.08, 129.53, 129.00,

124.03, 121.90, 120.56, 119.84. FTIR (ATR, cm^{-1}): 3041, 1609, 1575, 1557, 1498, 1463, 1398, 1377, 1338, 1314, 1263, 751.

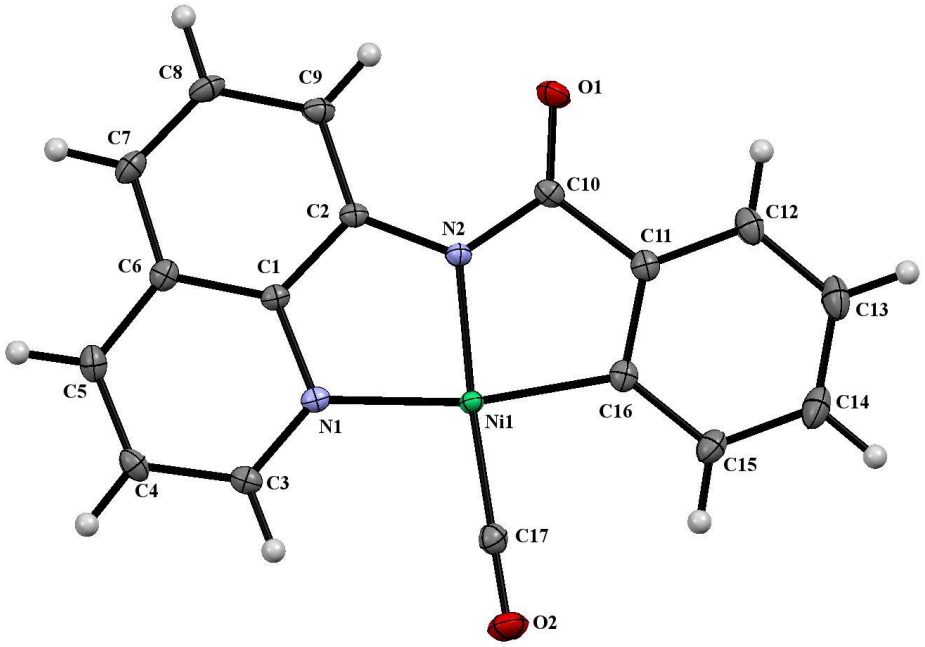
Synthesis of Ni(II) metallacycle by decarbonylation (11a). In a glovebox filled with N_2, the nickel metallacycle (**10a)** (332 mg, 1.00 mmol) was added to an oven dried 40 mL pressure tube with a stir bar. The $PhCH_3$ (20 ml) was added and the pressure tube was closed with a Teflon screw cap. The reaction mixture was then taken out of the glovebox and placed in a pre-heated oil bath at 160 °C for 2 h. After completion, the reaction mixture was taken out of the oil bath and allowed to cool to room temperature. The solution was allowed to sit undisturbed for a week while bright yellow crystals formed in solution. After the allotted time, the pressure tube was opened and the bright yellow crystals were isolated yielding **11a** in 33.4 mg (0.100 mmol, 10%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.77 (d, *J* = 7.8 Hz, 1H), 8.55 (d, *J* = 3.2 Hz, 1H), 8.37 (d, *J* = 8.4 Hz, 1H), 7.56 (t, *J* = 7.9 Hz, 1H), 7.50 (dd, *J* = 8.3, 4.9 Hz, 1H), 7.43 (d, *J* = 7.3 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.23 – 7.16 (m, 1H), 7.12 (dd, *J* = 4.7, 1.2 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, CD_2Cl_2) δ 186.96, 150.18, 147.46, 147.02, 146.70, 145.48, 140.29, 137.75, 131.76, 130.59, 130.01, 128.01, 127.18, 122.45, 119.35, 118.66. FTIR (ATR, cm^{-1}): 3050, 2063, 1634, 1573, 1501, 1466, 1385, 1340, 780. Elemental Analysis: calculated $C_{17}H_{10}N_2NiO_2$, C: 61.32; H: 3.03; N: 8.41; found, C: 61.37; H: 3.06; N: 8.48.



Before heating complex **10a** in $PhCH_3$.

After heating complex **10a** in $PhCH_3$.

Crystals of complex **11a**.



Perspective view of the molecular structure of $(C_{16}H_{10}N_2O)Ni(CO)$ (**11a**) with the atom labeling scheme for the non-hydrogen atoms. The thermal ellipsoids are scaled to enclose 50% probability.

Description of the X-ray Structural Analysis of $(C_{16}H_{10}N_2O)Ni(CO)$ (11a).

A long yellow parallelepiped crystal of $(C_{16}H_{10}N_2O)Ni(CO)$ (**11a**) was coated in polybutene oil (Sigma-Aldrich) and placed on the end of a MiTeGen loop. The sample was cooled to 100 K with an Oxford Cryostream 700 system and optically aligned on a Bruker AXS D8 Venture fixed-chi X-ray diffractometer equipped with a Triumph monochromator, a Mo Kα radiation source (λ = 0.71073 Å), and a PHOTON 100 CMOS detector. Three sets of 12 frames each were collected using the omega scan method with a 10 second exposure time. Integration of these frames followed by reflection indexing and least-squares refinement produced a crystal orientation matrix for the monoclinic crystal lattice that was used for the structural analysis.

Data collection consisted of the measurement of a total of 740 frames in four runs using omega scans with the detector held at 5.00 cm from the crystal. Frame scan parameters are summarized in Table 1 below:

Data collection details for $(C_{16}H_{10}N_2O)Ni(CO)$ (11a).

Run	2θ	ω	φ	χ	Scan Width (°)	Frames	Exposure Time (sec)
1	16.35	-166.34	-156.00	54.74	1.00	185	60.00
2	16.35	-166.34	-54.00	54.74	1.00	185	60.00
3	16.35	-166.34	-105.00	54.74	1.00	185	60.00
4	16.35	-166.34	153.00	54.74	1.00	185	60.00

The APEX3 software program (version 2016.9-0)[100] was used for diffractometer control, preliminary frame scans, indexing, orientation matrix calculations, least-squares refinement of cell parameters, and the data collection. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 29130 reflections to a maximum θ angle of 30.09° (0.71 Å resolution), of which 3891 were independent (average redundancy 7.487, completeness = 99.8%, R_{int} = 3.05%, R_{sig} = 1.96%) and 3417 (87.82%) were greater than $2\sigma(F^2)$. The final cell constants of a = 10.9298(5) Å, b = 7.1659(3) Å, c = 17.2345(7) Å, β = 101.0570(10)°, volume = 1324.78(10) $Å^3$, are based upon the refinement of the XYZ-centroids of 9902 reflections above 20 σ(I) with 6.174° < 2θ < 60.11°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.859. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.541 and 0.921.

The structure was solved by using the intrinisic phasing routine available in the APEX3 software[100] and refined using the programs provided by SHELXL-2014/7.[101] The crystallographic asymmetric unit consists of only a molecule of $(C_{16}H_{10}N_2O)Ni(CO)$ (**13a**). Idealized positions for the aromatic hydrogen atoms were included as fixed contributions using a riding model with isotropic temperature factors set at 1.2 times that of the adjacent carbon atom. Full-matrix least-squares refinement, based upon the minimization of $\Sigma w_i |F_o^2 - F_c^2|^2$, with weighting $w_i^{-1} = [\sigma^2(F_o^2) + (0.0254\ P)^2 + 1.0711\ P]$, where $P = (\text{Max}\ (F_o^2, 0) + 2\ F_c^2)/3$.[101] The final anisotropic full-matrix least-squares refinement on F^2 with 199 variables converged at R1 = 2.48 % for the 3417 data with $I>2\sigma(I)$ and wR2 = 6.11 % for all data. The goodness-of-fit was 1.033.[101] A correction for secondary extinction was not applied. The largest peak in the final difference electron

density synthesis was 0.537 $e^-/Å^3$ and the largest hole was -0.290 $e^-/Å^3$ with an RMS deviation of 0.063 $e^-/Å^3$. The linear absorption coefficient, atomic scattering factors, and anomalous dispersion corrections were calculated from values found in the International Tables of X-ray Crystallography.[103]

Crystal data for ($C_{16}H_{10}N_2O$)Ni(CO) (11a).

Ident. code	jh54cms	
Chem. form.	$C_{17}H_{10}N_2NiO_2$	
Mol. weight	332.98 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.057 x 0.120 x 0.476 mm	
Cryst. type	monoclinic	
Space group	$P2_1/c$ (No. 14)	
Unit cell	a = 10.9298(5) Å	α = 90°
	b = 7.1659(3) Å	β = 101.0570(10)°
	c = 17.2345(7) Å	γ = 90°
Volume, $Å^3$	1324.78(10)	
Z	4	
Density (calc)	1.669 g/cm^3	
Abs. coeff.	1.472 mm^{-1}	
F(000)	680	

Data collection and structure refinement for ($C_{16}H_{10}N_2O$)Ni(CO) (11a).

Theta range	3.09 to 30.09°
Index ranges	$-15 \le h \le 15$, $-10 \le k \le 10$, $-22 \le l \le 24$
Reflections	29130
Independent refls	3891 [R(int) = 0.0305]
Coverage	99.8%
Abs. correction	multi-scan
Max./ min. trans.	0.921 and 0.541
Refinement method	Full-matrix least-squares on F^2
Ref. program	SHELXL-2014/7 (Sheldrick, 2014)
Data / restrs / parms	3891 / 0 / 199

GOF on F^2	1.033	
Final R indices	3417 data; $I>2\sigma(I)$	R1 = 0.0248, wR2 = 0.0586
	all data	R1 = 0.0319, wR2 = 0.0611
Largest diff. peak and hole	0.537 and -0.290 $e^-/Å^3$	

Atomic coordinates and equivalent isotropic atomic displacement parameters ($Å^2$) for ($C_{16}H_{10}N_2O$)Ni(CO) (11a). U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U(eq)
Ni1	0.39088(2)	0.71655(2)	0.50851(2)	0.00949(5)
O1	0.49582(10)	0.57634(15)	0.30799(6)	0.0178(2)
O2	0.22921(10)	0.71492(16)	0.62317(7)	0.0227(2)
N1	0.54072(10)	0.81810(15)	0.57288(6)	0.0102(2)
N2	0.48904(10)	0.69556(15)	0.43209(6)	0.0104(2)
C1	0.63842(12)	0.82426(18)	0.53303(7)	0.0102(2)
C2	0.61147(12)	0.75649(17)	0.45385(7)	0.0103(2)
C3	0.55955(12)	0.88152(18)	0.64668(8)	0.0126(2)
C4	0.67458(13)	0.95435(19)	0.68502(8)	0.0148(3)
C5	0.77259(13)	0.9592(2)	0.64618(8)	0.0157(3)
C6	0.75693(12)	0.89248(18)	0.56750(8)	0.0126(2)
C7	0.85140(13)	0.8925(2)	0.52158(9)	0.0164(3)
C8	0.82440(13)	0.8296(2)	0.44511(9)	0.0164(3)
C9	0.70522(13)	0.76201(19)	0.41003(8)	0.0137(2)
C10	0.43969(12)	0.61425(18)	0.36133(7)	0.0119(2)
C11	0.30521(12)	0.57602(18)	0.35883(8)	0.0121(2)

	x/a	y/b	z/c	U(eq)
C12	0.22833(13)	0.5061(2)	0.29162(8)	0.0171(3)
C13	0.10260(14)	0.4776(2)	0.29229(9)	0.0222(3)
C14	0.05619(13)	0.5201(2)	0.35963(10)	0.0220(3)
C15	0.13410(13)	0.5897(2)	0.42726(9)	0.0169(3)
C16	0.26083(12)	0.61852(18)	0.42801(8)	0.0126(2)
C17	0.29259(13)	0.7178(2)	0.57821(8)	0.0148(3)

Interatomic distances (Å) for ($C_{16}H_{10}N_2O$)Ni(CO) (11a).

Ni1-C17	1.7584(14)	Ni1-N2	1.8574(11)
Ni1-C16	1.9189(13)	Ni1-N1	1.9354(11)
O1-C10	1.2294(16)	O2-C17	1.1344(17)
N1-C3	1.3290(17)	N1-C1	1.3766(16)
N2-C10	1.3658(17)	N2-C2	1.3890(16)
C1-C6	1.4052(18)	C1-C2	1.4250(18)
C2-C9	1.3852(17)	C3-C4	1.4039(19)
C4-C5	1.368(2)	C5-C6	1.4168(19)
C6-C7	1.4163(19)	C7-C8	1.370(2)
C8-C9	1.4125(19)	C10-C11	1.4876(18)
C11-C12	1.3878(19)	C11-C16	1.4041(18)
C12-C13	1.392(2)	C13-C14	1.387(2)
C14-C15	1.397(2)	C15-C16	1.3980(19)

Bond angles (°) for ($C_{16}H_{10}N_2O$)Ni(CO) (11a).

C17-Ni1-N2	175.14(6)	C17-Ni1-C16	91.77(6)
N2-Ni1-C16	84.62(5)	C17-Ni1-N1	99.62(6)

N2-Ni1-N1	84.06(5)	C16-Ni1-N1	168.56(5)
C3-N1-C1	118.29(11)	C3-N1-Ni1	129.48(9)
C1-N1-Ni1	112.22(8)	C10-N2-C2	124.76(11)
C10-N2-Ni1	119.00(9)	C2-N2-Ni1	116.15(8)
N1-C1-C6	122.72(12)	N1-C1-C2	115.41(11)
C6-C1-C2	121.86(12)	C9-C2-N2	129.56(12)
C9-C2-C1	118.27(12)	N2-C2-C1	112.16(11)
N1-C3-C4	122.54(12)	C5-C4-C3	119.57(12)
C4-C5-C6	119.84(13)	C1-C6-C7	118.40(12)
C1-C6-C5	117.02(12)	C7-C6-C5	124.58(13)
C8-C7-C6	119.45(13)	C7-C8-C9	122.37(13)
C2-C9-C8	119.63(13)	O1-C10-N2	126.42(12)
O1-C10-C11	124.72(12)	N2-C10-C11	108.86(11)
C12-C11-C16	122.32(13)	C12-C11-C10	121.83(12)
C16-C11-C10	115.84(11)	C11-C12-C13	119.13(14)
C14-C13-C12	119.68(14)	C13-C14-C15	120.96(14)
C14-C15-C16	120.32(14)	C15-C16-C11	117.59(12)
C15-C16-Ni1	131.00(11)	C11-C16-Ni1	111.39(9)
O2-C17-Ni1	178.66(13)		

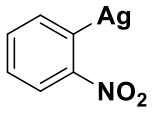
Anisotropic atomic displacement parameters ($Å^2$) for ($C_{16}H_{10}N_2O$)Ni(CO) (11a). The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$.

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Ni1	0.00930(8)	0.01046(8)	0.00940(8)	-0.00005(6)	0.00354(6)	-0.00031(6)
O1	0.0215(5)	0.0220(5)	0.0112(4)	-0.0029(4)	0.0063(4)	-0.0029(4)
O2	0.0223(5)	0.0265(6)	0.0232(5)	-0.0018(5)	0.0140(4)	-0.0033(5)
N1	0.0111(5)	0.0088(5)	0.0113(5)	0.0018(4)	0.0036(4)	0.0011(4)
N2	0.0102(5)	0.0123(5)	0.0092(5)	0.0002(4)	0.0028(4)	-0.0007(4)
C1	0.0114(5)	0.0082(5)	0.0114(6)	0.0016(4)	0.0036(4)	0.0006(4)
C2	0.0116(5)	0.0088(6)	0.0111(6)	0.0008(4)	0.0038(4)	0.0010(4)
C3	0.0159(6)	0.0108(6)	0.0113(6)	0.0012(5)	0.0035(5)	0.0018(5)
C4	0.0203(7)	0.0129(6)	0.0102(6)	0.0002(5)	0.0009(5)	-0.0007(5)
C5	0.0156(6)	0.0145(6)	0.0151(6)	0.0007(5)	-0.0015(5)	-0.0027(5)
C6	0.0127(6)	0.0103(6)	0.0145(6)	0.0024(5)	0.0021(5)	-0.0002(5)
C7	0.0116(6)	0.0169(6)	0.0213(7)	0.0013(5)	0.0044(5)	-0.0024(5)
C8	0.0142(6)	0.0159(6)	0.0217(7)	0.0014(5)	0.0097(5)	-0.0007(5)
C9	0.0162(6)	0.0121(6)	0.0144(6)	-0.0002(5)	0.0070(5)	-0.0008(5)
C10	0.0152(6)	0.0103(6)	0.0100(5)	0.0015(4)	0.0023(5)	0.0002(5)
C11	0.0137(6)	0.0092(6)	0.0129(6)	0.0014(5)	0.0012(5)	0.0006(5)
C12	0.0187(7)	0.0153(6)	0.0153(6)	-0.0001(5)	-0.0019(5)	0.0007(5)
C13	0.0182(7)	0.0213(7)	0.0231(7)	-0.0024(6)	-0.0064(6)	0.0002(6)
C14	0.0118(6)	0.0208(7)	0.0313(8)	-0.0004(6)	-0.0011(6)	-0.0008(5)
C15	0.0125(6)	0.0158(6)	0.0224(7)	0.0004(5)	0.0035(5)	0.0006(5)
C16	0.0129(6)	0.0094(6)	0.0150(6)	0.0012(5)	0.0015(5)	0.0002(5)
C17	0.0151(6)	0.0128(6)	0.0166(6)	-0.0010(5)	0.0030(5)	-0.0014(5)

U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}

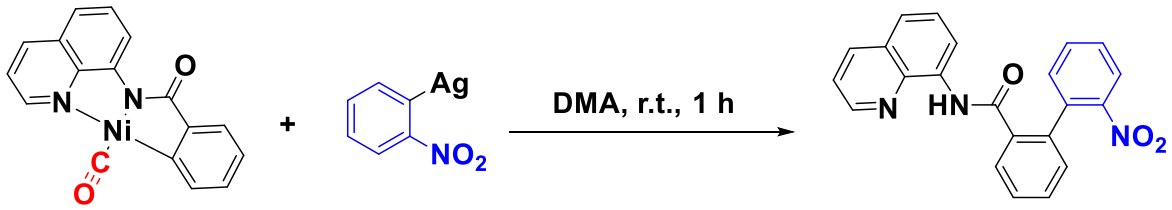
Hydrogen atom coordinates and isotropic atomic displacement parameters ($Å^2$) for ($C_{16}H_{10}N_2O$)Ni(CO) (11a).

	x/a	y/b	z/c	U(eq)
H3	0.4926	0.8774	0.6746	0.015
H4	0.6843	1.0000	0.7376	0.018
H5	0.8509	1.0071	0.6719	0.019
H7	0.9328	0.9358	0.5436	0.02
H8	0.8881	0.8316	0.4146	0.02
H9	0.6894	0.7205	0.3567	0.016
H12	0.2611	0.4780	0.2457	0.021
H13	0.0488	0.4293	0.2468	0.027
H14	-0.0298	0.5016	0.3598	0.026
H15	0.1008	0.6175	0.4730	0.02



Synthesis of (2-nitrophenyl)silver (12a). The title compound was prepared by following literature synthesis.[104] To a mixture of AgF (269 mg, 2.12 mmol) and anhydrous MeCN (20 mL) in a glovebox filled with N_2, was added a solution of 5,5-dimethyl-2-(2-nitrophenyl)-[1,3,2]dioxaborinane (499 mg, 2.12 mmol) in MeCN (20 mL). The reaction mixture was stirred at room temperature for 24 h while protected from light with aluminum foil. The solid was collected by filtration and washed with diethyl ether (~50 mL), to yield 316 mg (1.37 mmol, 65%) as a bright yellow solid. ^{1}H NMR (400 MHz,

DMSO-d_6) δ 8.03 (dd, J = 8.1, 1.2 Hz, 1H), 7.95 (dd, J = 7.0, 1.7 Hz, 1H), 7.54 (td, J = 7.1, 1.3 Hz, 1H), 7.40 (td, J = 8.4, 8.0, 1.7 Hz, 1H).



11a **12a** **13a**

Procedure for (hetero)arylation of complex 11a with silver aryls. To a mixture of complex **11a** (8.3 mg, 0.025 mmol) and anhydrous DMA (1 mL) in a glovebox filled with N_2, was added a solution of (2-nitrophenyl)silver(I) (0.025 mmol or 0.050 mmol) in anhydrous DMA (1 mL) dropwise. The mixture was stirred at room temperature for 1 h. The reaction mixture was taken out of the glovebox and poured into a 100 mL separatory funnel. To the solution, water (25 mL), aqueous HCl (2N, 3 mL) were added and extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with water (3 x 30 mL) and brine (~15 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. Then 1,3,5-trimethoxybenzene (2.0 mg) was added to the residue and the crude mixture was dissolved in $CDCl_3$ for ^1H analysis.

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